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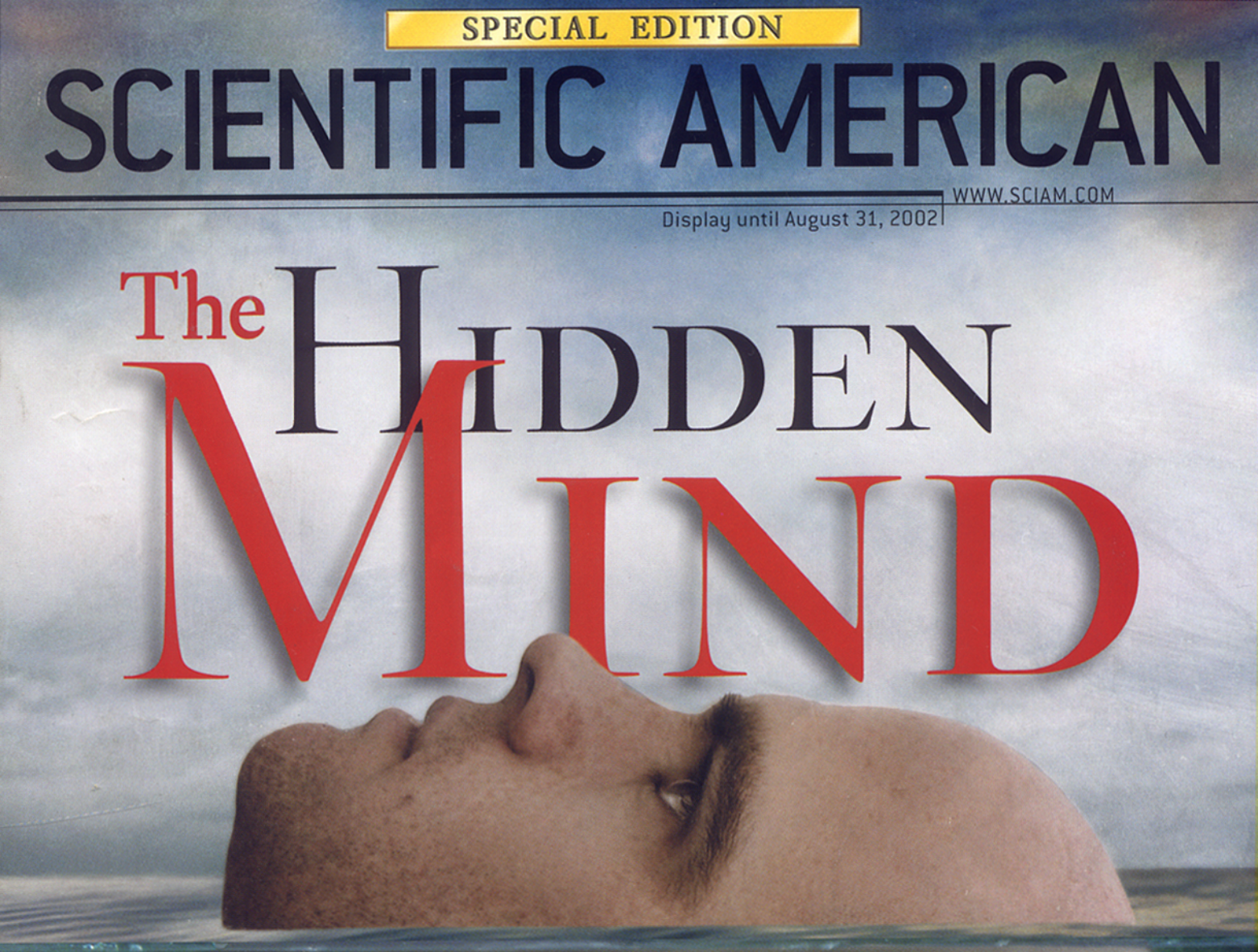

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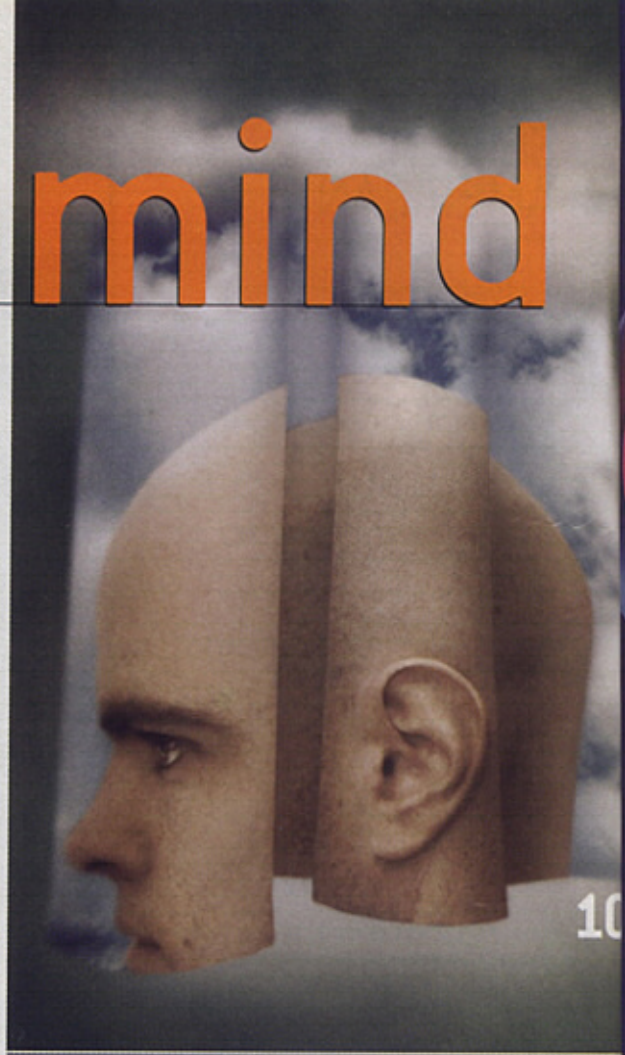

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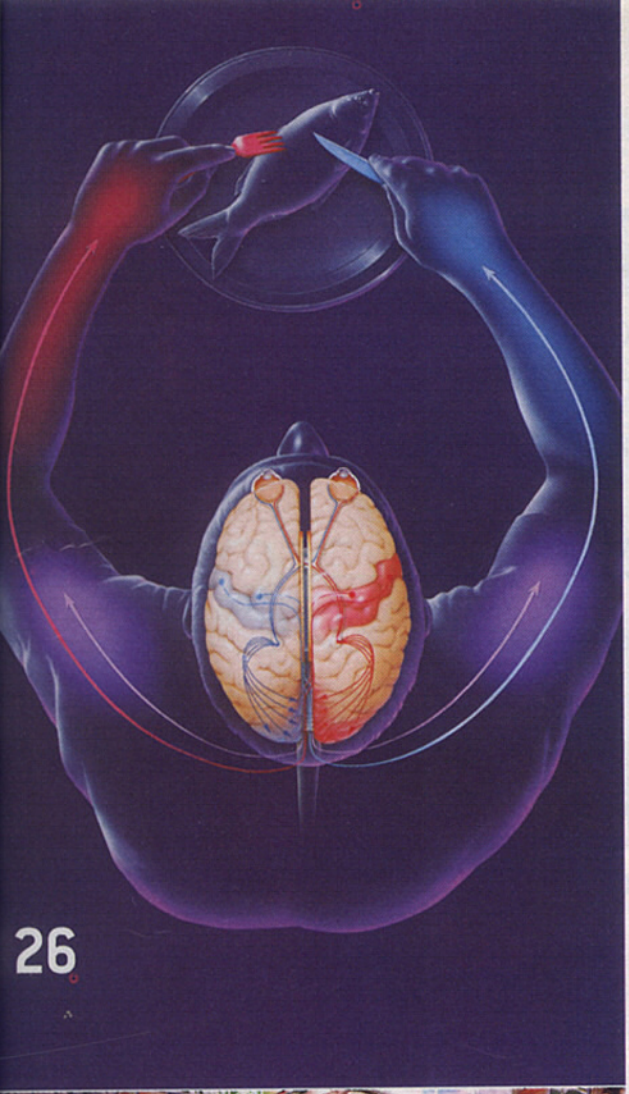

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Cover illustration by Melissa Szalkowski

Scientific American Special (ISSN 1048-0943), Volume 12, Number 1, 2002, published by Scientific American, Inc., 415 Madison Avenue, New York, NY 10017-1111.

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Periodicals Publication Rate. Postage paid at New York, N.Y., and at additional mailing offices. Canadian BN No. 127387652RT; QST No. Q1015332537. To purchase additional quantities: 1 to 9 copies: U.S. $5.95 each plus $2.00 per copy for postage and handling (outside U.S. $5.00 P&H). Send payment to Scientific American, Dept. THM, 415 Madison Avenue, New York, NY 10017-1111. Inquiries: Fax 212-355-0408 or telephone 212-451-8890. Printed in U.S.A.

How the Brain Creates the Mind

We have long wondered how the conscious mind comes to be. Greater understanding of brain function ought to lead to an eventual solution

By Antonio R. Damasio

At the start of the new millennium, it is apparent that one question towers above all others in life sciences: How does the set of processes we call mind emerge from the activity of the organ we call brain? The question is hardly new. It has been formulated in one way or another for centuries. Once it became possible to pose the question and not be burned at the stake, it has been asked openly and insistently. Recently the question has preoccupied both the experts—neuroscientists, cognitive scientists and philosophers—and others who wonder about the origin of the mind, specifically the conscious mind.

The question of consciousness now occupies center stage because biology in general and neuroscience in particular have been so remarkably successful at unraveling a great many of life's secrets. More may have been learned about the brain and the mind in the 1990s—the so-called decade of the brain—than during the entire previous history of psychology and neuroscience. Elucidating the neurobiological basis of the conscious mind—a version of the classic mind-body problem—has become almost a residual challenge.

Contemplation of the mind may induce timidity in the contemplator, especially when consciousness becomes the focus of the inquiry. Some thinkers, expert and amateur alike, believe the question may be unanswerable in principle. For others, the relentless and exponential increase in new knowledge may give rise to a vertiginous feeling that no problem can resist the assault of science if only the theory is right and the techniques are powerful enough. The debate is intriguing and even unexpected, as no comparable doubts have been raised over the likelihood of explaining how the brain is responsible for processes such as vision or memory, which are obvious components of the larger process of the conscious mind.

I am firmly in the confident camp: a substantial explanation for the mind's emergence from the brain will be produced and perhaps soon. The giddy feeling, however, is tempered by the acknowledgment of some sobering difficulties.

Nothing is more familiar than the mind. Yet the pilgrim in search of the sources and mechanisms behind the mind embarks on a journey into a strange and exotic landscape. In no particular order, what follows are the main problems facing those who seek the biological basis for the conscious mind.

The first quandary involves the perspective one must adopt to study the conscious mind in relation to the brain in which we believe it originates. Anyone's body and brain are observable to third parties; the mind, though, is observable only to its owner. Multiple individuals confronted with the same body or brain can make the same observations of that body or brain, but no comparable direct third-person observation is possible for anyone's mind. The body and its brain are public, exposed, external and unequivocally objective entities. The mind is a private, hidden, internal, unequivocally subjective entity.

How and where then does the dependence of a first-person mind on a third-person body occur precisely? Techniques used to study the brain include refined brain scans and the measurement of patterns of activity in the brain's neurons. The naysayers argue that the exhaustive compilation of all these data adds up to *correlates* of mental states but nothing resembling an *actual mental state*. For them, detailed observation of living matter thus leads not to mind but simply to the details of living mat-

MULTIMEDIA MIND-SHOW occurs constantly as the brain processes external and internal sensory events. As the brain answers the unasked question of who is experiencing the mind-show, the sense of self emerges.

SLIM FILMS

Updated from the December 1999 issue

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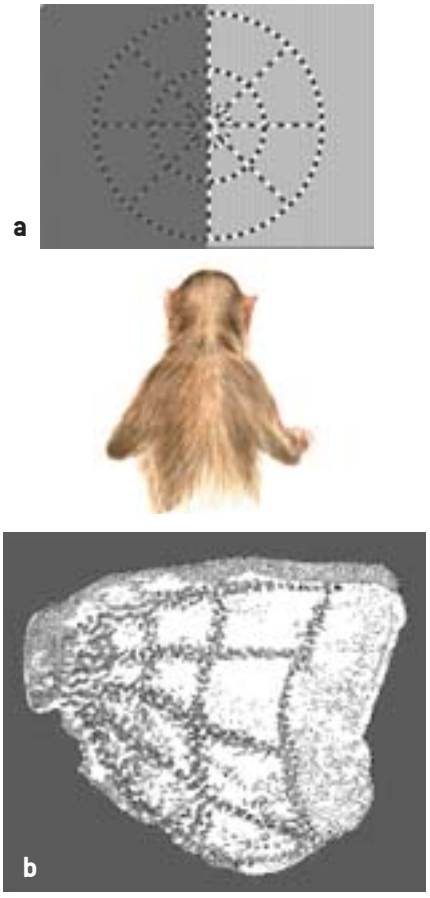
ter. The understanding of how living matter generates the sense of self that is the hallmark of a conscious mind—the sense that the images in my mind are mine and are formed in my perspective—is simply not possible. This argument, though incorrect, tends to silence most hopeful investigators of the conscious mind.

To the pessimists, the conscious-mind problem seems so intractable that it is not even possible to explain why the mind is even *about* something—why mental processes represent internal states or interactions with external objects. (Philosophers refer to this representational quality of the mind with the confusing term "intentionality.") This argument is false.

The final negative contention is the reminder that elucidating the emergence of the conscious mind depends on the existence of that same conscious mind. Conducting an investigation with the very instrument being investigated makes both the definition of the problem and the approach to a solution especially complicated. Given the conflict between observer and observed, we are told, the human intellect is unlikely to be up to the task of comprehending how mind emerges from brain. This conflict is real, but the notion that it is insurmountable is inaccurate.

In summary, the apparent uniqueness of the conscious-mind problem and the difficulties that complicate ways to get at that problem generate two effects: they frustrate those researchers committed to finding a solution and confirm the conviction of others who intuitively believe that a solution is beyond our reach.

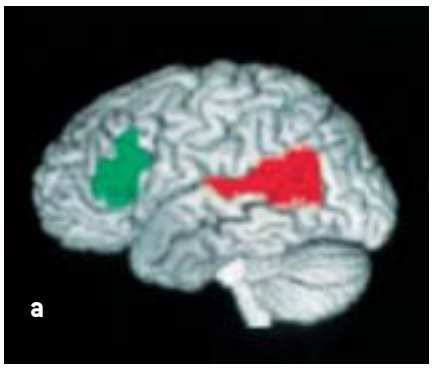


BRAIN'S BUSINESS is representing other things. Studies with macaques show a remarkable fidelity between a seen shape (*a*) and the shape of the neural activity pattern (*b*) in one of the layers of the primary visual cortex.

Evaluating the Difficulties

THOSE WHO CITE the inability of research on the living matter of the brain to reveal the "substance of mind" assume that the current knowledge of that living matter is sufficient to make such judgment final. This notion is entirely unacceptable. The current description of neurobiological phenomena is quite incomplete, any way you slice it. We have yet to resolve numerous details about the function of neurons and circuits at the molecular level; we do not yet grasp the behavior of populations of neurons within a local brain region; and our understanding of the large-scale systems made up of multiple brain regions is also incomplete. We are barely beginning to address the fact that interactions among many noncontiguous brain regions probably yield highly complex biological states that are vastly more than the sum of their parts.

In fact, the explanation of the physics related to biological events is still incomplete. Consequently, declaring the conscious-mind problem insoluble because we have studied the brain to the hilt and have not found the mind is ludicrous. We have not yet fully studied either neurobiology or its related physics. For example, at the finest level of description of mind, the swift construction, manipulation and superposition of many sensory images might require explanation at the quantum level. Incidentally, the notion of a possible role for quantum physics in the elucidation of mind, an idea usually associated with mathematical physicist Roger Penrose of the University of Oxford, is not an endorsement of his specific proposals, namely that consciousness is based on quantum-level phenomena occurring in the microtubules—constituents of neurons and other cells. The quantum level of operations might help explain how we have a mind, but I regard it as unnecessary to explain how we *know* that we own that mind—the issue I regard as most critical for a comprehensive account of consciousness.



NEUROSCIENCE continues to associate specific brain structures with specific tasks. Some language regions are highlighted in *a* and *b*. Color-processing (*red*) and face-processing (*green*) regions are shown in *c*. One's own body sense depends on the region shown in *d*.

The strangeness of the conscious-mind problem mostly reflects ignorance, which limits the imagination and has the curious effect of making the possible seem impossible. Science-fiction writer Arthur C. Clarke has said, "Any sufficiently advanced technology is indistinguishable from magic." The "technology" of the brain is so complex as to appear magical, or at least unknowable. The appearance of a gulf between mental states and physical/biological phenomena comes from the large disparity between two bodies of knowledge—the good understanding of mind we have achieved through centuries of introspection and the efforts of cognitive science versus the incomplete neural specification we have achieved through the efforts of neuroscience. But there is no reason to expect that neurobiology cannot bridge the gulf. Nothing indicates that we have reached the edge of an abyss that would separate,

DIMITRY SCHIDLOVSKY; SOURCE: TOOTELL ET AL., IN *JOURNAL OF NEUROSCIENCE*, MAY 1988 (*left*); HANNA DAMASIO (*above* and *opposite page*)

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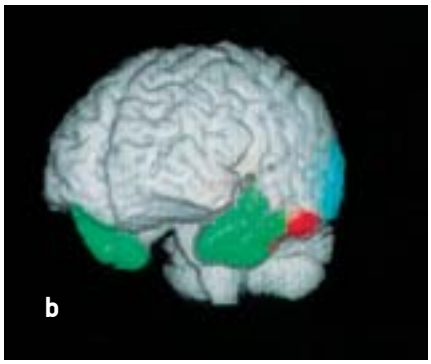

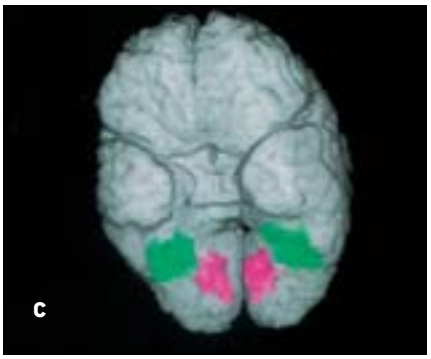

in principle, the mental from the neural.

Therefore, I contend that the biological processes now presumed to correspond to mind processes in fact *are* mind processes and will be seen to be so when understood in sufficient detail. I am not denying the existence of the mind or saying that once we know what we need to know about biology the mind ceases to exist. I simply believe that the private, personal mind, precious and unique, indeed *is* biological and will one day be described in terms both biological and mental.

The other main objection to an understanding of mind is that the real conflict between observer and observed makes the human intellect unfit to study itself. It is important, however, to point out that the brain and mind are not a monolith: they have multiple structural levels, and the highest of those levels creates instruments that permit the observation of the other levels. For example, language endowed the mind with the power to categorize and manipulate knowledge according to logical principles, and that helps us classify observations as true or false. We should be modest about the likelihood of ever observing our entire nature. But declaring defeat before we even make the attempt defies Aristotle's observation that human beings are infinitely curious about their own nature.

Reasons for Optimism

MY PROPOSAL for a solution to the conundrum of the conscious mind requires breaking the problem into two parts. The first concern is how we generate what I call a "movie-in-the-brain." This "movie" is a metaphor for the integrated and unified composite of diverse sensory images—visual, auditory, tactile, olfactory and others—that constitutes the multimedia show we call mind. The second issue is the "self" and how we automatically generate a sense of ownership for the movie-in-the-brain. The two parts of the problem are related, with the latter nested in the former. Separating them is a useful research strategy, as each requires its own solution.

Neuroscientists have been attempting unwittingly to solve the movie-in-the-brain part of the conscious-mind problem for most of the history of the field. The endeavor of mapping the brain regions involved in constructing the movie began almost a century and a half ago, when Paul Broca and Carl Wernicke first suggested that different regions of the brain were involved in processing different aspects of language. More recently, thanks to the advent of ever more sophisticated tools, the effort has begun to reap handsome rewards.

Researchers can now directly record the activity of a single neuron or group of neurons and relate that activity to aspects of a specific mental state, such as the perception of the color red or of a curved line. Brain-imaging techniques such as PET (positron emission tomography) scans and fMR (functional magnetic resonance) scans reveal how different brain regions in a normal, living person are engaged by a certain mental effort, such as relating a word to an object or learning a particular face. Investigators can determine how molecules within microscopic neuron circuits participate in such diverse mental tasks, and they can identify the genes necessary for the production and deployment of those molecules.

Progress in this field has been swift ever since David H. Hubel and Torsten Wiesel of Harvard University provided the first clue for how brain circuits represent the shape of a given object, by demonstrating that neurons in the primary visual cortex were selectively tuned to respond to edges oriented in varied angles. Hubel and Margaret S. Livingstone, also at Harvard, later showed that other neurons in the primary visual cortex respond selectively to color but not shape. And Semir Zeki of University College London found that brain regions that received sensory information after the primary visual cortex did were specialized for the further processing of color or movement. These results provided a counterpart to observations made in living neurological patients: damage to distinct regions of the visual cortices interferes with color perception while leaving discernment of shape and movement intact.

A large body of work, in fact, now points to the existence of a correspon-

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ANTONIO R. DAMASIO is M. W. Van Allen Distinguished Professor and head of the department of neurology at the University of Iowa College of Medicine and adjunct professor at the Salk Institute for Biological Studies in San Diego. He was born in Portugal and received his M.D. and Ph.D. from the University of Lisbon. With his wife, Hanna, Damasio created a facility at Iowa dedicated to the investigation of neurological disorders of mind and behavior. A member of the Institute of Medicine of the National Academy of Sciences and of the American Academy of Arts and Sciences, Damasio is the author of *Descartes' Error: Emotion, Reason, and the Human Brain* (1994), *The Feeling of What Happens: Body and Emotion in the Making of Consciousness* (1999) and *Looking for Spinoza* (forthcoming).

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dence between the structure of an object as taken in by the eye and the pattern of neuron activity generated within the visual cortex of the organism seeing that object [*see illustration on page 6*].

Further remarkable progress involving aspects of the movie-in-the-brain has led to increased insights related to mechanisms of learning and memory. In rapid succession, research has revealed that the brain uses discrete systems for different types of learning. The basal ganglia and cerebellum are critical for the acquisition of skills—for example, learning to ride a bicycle or play a musical instrument. The hippocampus is integral to the learning of facts pertaining to such entities as people, places or events. And once facts are learned, the long-term memory of those facts relies on multicomponent brain systems, whose key parts are located in the vast brain expanses known as cerebral cortices.

Moreover, the process by which newly learned facts are consolidated in long-term memory goes beyond properly working hippocampi and cerebral cortices. Certain processes must take place, at the level of neurons and molecules, so that the neural circuits are etched, so to speak, with the impressions of a newly learned fact. This etching depends on strengthening or weakening the contacts between neurons, known as synapses. A provocative finding by Eric R. Kandel of Columbia University and Timothy P. Tully of Cold Spring Harbor Laboratory is that etching the impression requires the synthesis of fresh proteins, which in turn relies on the engagement of specific genes within the neurons charged with supporting the consolidated memory.

These brief illustrations of progress could be expanded with other revelations from the study of language, emotion and decision making. Whatever mental function we consider, it is possible to identify distinct parts of the brain that contribute to the production of a function by working in concert; a close correspondence exists between the appearance of a mental state or behavior and the activity of selected brain regions. And that correspondence can be established between a given macroscopically identifiable region (for example, the primary visual cortex, a language-related area or an emotion-related nucleus) and the microscopic neuron circuits that constitute the region.

Most exciting is that these impressive advances in the study of the brain are a mere beginning. New analytical techniques continuously improve the ability to study neural function at the molecular level and to investigate the highly complex large-scale phenomena arising from the whole brain. Revelations from those two areas will make possible ever finer correspondences between brain states and mental states, between brain and mind. As technology develops and the ingenuity of researchers grows, the fine grain of physical structures and biological activities that constitute the movie-in-the-brain will gradually come into focus.

Confronting the Self

THE MOMENTUM of current research on cognitive neuroscience, and the sheer accumulation of powerful facts, may well convince many doubters that the neural basis for the movie-in-the-brain can be identified. But the skeptics will still find it difficult to accept that the second part of the conscious-mind problem—the emergence of a sense of self—can be solved at all. Although I grant that solving this part of the problem is by no means obvious, a possible solution has been proposed, and a hypothesis is being tested.

The main ideas behind the hypothesis involve the unique representational ability of the brain. Cells in the kidney or liver perform their assigned functional roles and do not represent any other cells or functions. But brain cells, at every level of the nervous system, represent entities or events occurring elsewhere in the organism. Brain cells are assigned by design to be *about* other things and other doings. They are born cartographers of the geography of an organism and of the events that take place within that geography. The oft-quoted mystery of the "intentional" mind relative to the representation of external objects turns out to be no mystery at all. The philosophical despair that surrounds this "intentionality" hurdle alluded to earlier—why mental states represent internal emotions or interactions with external objects—lifts with the consideration of the brain in a Darwinian context: evolution has crafted a brain that is in the business of directly representing the organism and indirectly representing whatever the organism interacts with.

The brain's natural intentionality then takes us to another established fact: the brain possesses devices within its structure that are designed to manage the life of the organism in such a way that the internal chemical balances indispensable for survival are maintained at all times. These devices are neither hypothetical nor abstract; they are located in the brain's core, the brain stem and hypothalamus. The brain devices that regulate life also represent, of necessity, the constantly changing states of the organism as they occur. In other words, the brain has a natural means to represent the structure and state of the *whole* living organism.

But how is it possible to move from such a biological self to the sense of ownership of one's thoughts, the sense that one's thoughts are constructed in one's own perspective, without falling into the trap of invoking an all-knowing homunculus who interprets one's reality? How is it possible to know about self and surroundings? I have argued in my book *The Feeling of What Happens* that the biological foundation for the sense of self can be found in those brain devices that represent, moment by moment, the continuity of the same individual organism.

Simply put, my hypothesis suggests

The pilgrim in search of the mechanisms of the mind journeys into A STRANGE, EXOTIC LANDSCAPE.

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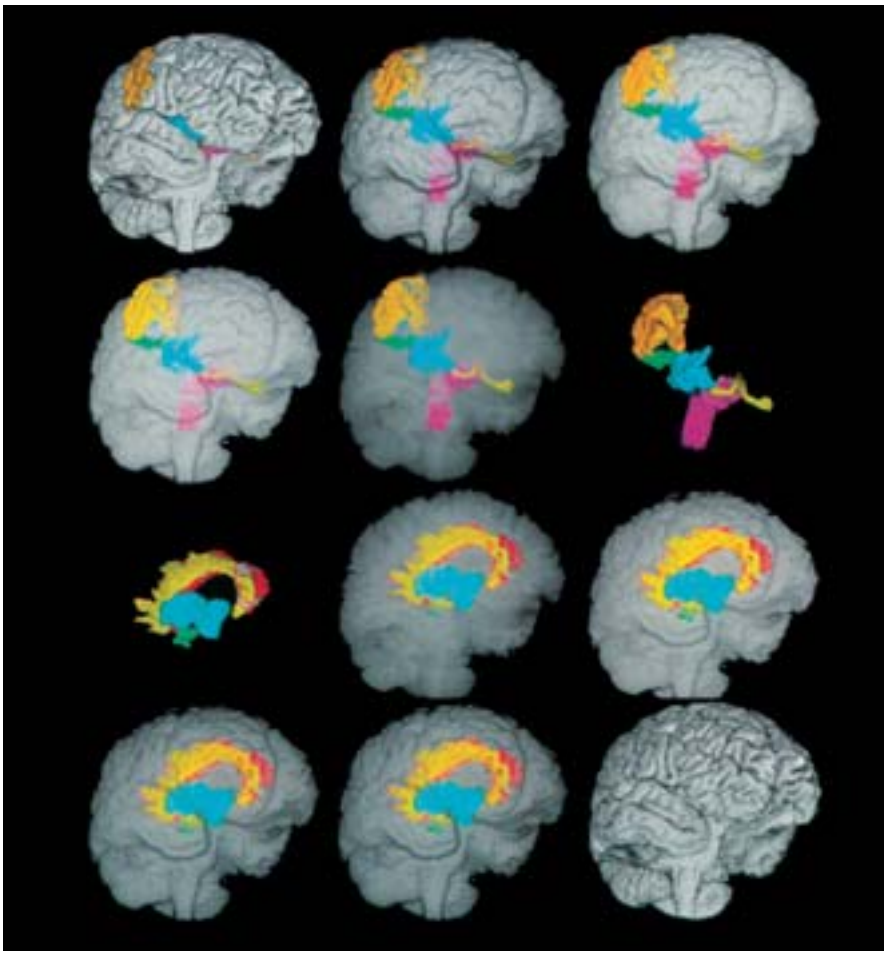
that the brain uses structures designed to map both the organism and external objects to create a fresh, second-order representation. This representation indicates that the organism, as mapped in the brain, is involved in interacting with an object, also mapped in the brain. The second-order representation is no abstraction; it occurs in neural structures such as the thalamus and the cingulate cortices.

Such newly minted knowledge adds important information to the evolving mental process. Specifically, it *presents* within the mental process the information that the organism is the owner of the mental process. It volunteers an answer to a question never posed: To whom is this happening? The sense of a self in the act of knowing is thus created, and that forms the basis for the first-person perspective that characterizes the conscious mind.

Again from an evolutionary perspective, the imperative for a sense of self becomes clear. As Willy Loman's wife says in Arthur Miller's *Death of a Salesman*: "Attention must be paid!" Imagine a self-aware organism versus the same type of organism lacking it. A self-aware organism has an incentive to heed the alarm signals provided by the movie-in-the-brain (for instance, pain caused by a particular object) and plan the future avoidance of such an object. Evolution of self rewards awareness, which is clearly a survival advantage.

With the movie metaphor in mind, if you will, my solution to the conscious-mind problem is that the sense of self in the act of knowing emerges *within* the movie. Self-awareness is actually part of the movie and thus creates, within the same frame, the "seen" and the "seer," the "thought" and the "thinker." There is no separate spectator for the movie-in-the-brain. The idea of spectator is constructed within the movie, and no ghostly homunculus haunts the theater. Objective brain processes knit the subjectivity of the conscious mind out of the cloth of sensory mapping. And because the most fundamental sensory mapping pertains to body states and is imaged as feelings, the sense of self in the act of knowing emerges as a special kind of feeling—the feeling of what happens in an organism caught in the act of interacting with an object.



THE SENSE OF SELF has a seat in the core of the brain. Stripping away the external anatomy of a human brain shows a number of deep-seated regions responsible for homeostatic regulation, emotion, wakefulness and the sense of self.

The Future

I WOULD BE FOOLISH to make predictions about what can and cannot be discovered or about when something might be discovered and the route of a discovery. Nevertheless, it is probably safe to say that by 2050 sufficient knowledge of biological phenomena will have wiped out the traditional dualistic separations of body/brain, body/mind and brain/mind.

Some observers may fear that by pinning down its physical structure something as precious and dignified as the human mind may be downgraded or vanish entirely. But explaining the origins and workings of the mind in biological tissue will not do away with the mind, and the awe we have for it can be extended to the amazing microstructure of the organism and to the immensely complex functions that allow such a microstructure to generate the mind. By understanding the mind at a deeper level, we will see it as nature's most complex set of biological phenomena rather than as a mystery with an unknown nature. The mind will survive explanation, just as a rose's perfume, its molecular structure deduced, will still smell as sweet. SA

MORE TO EXPLORE

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HANNA DAMASIO

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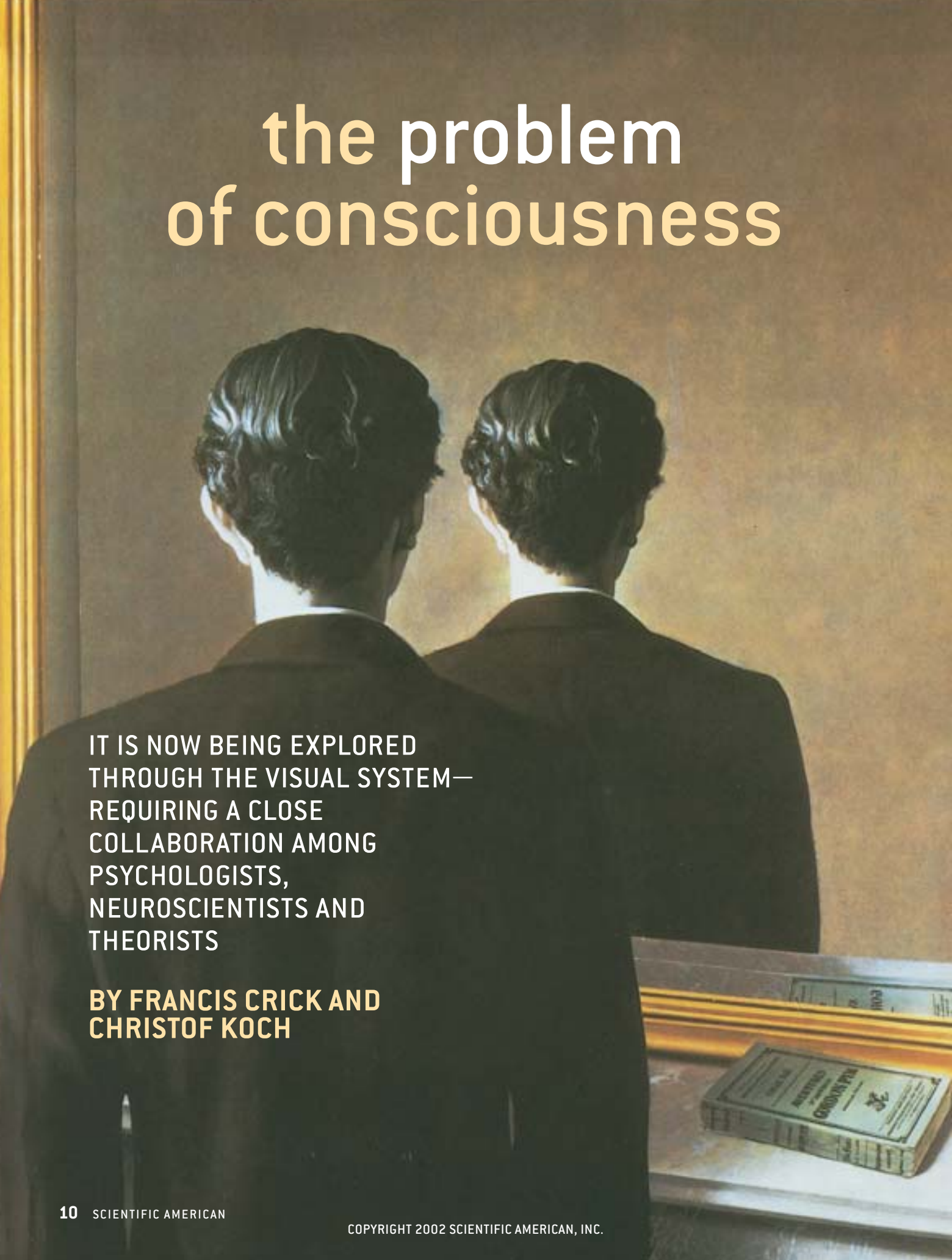
the problem of consciousness



IT IS NOW BEING EXPLORED THROUGH THE VISUAL SYSTEM—REQUIRING A CLOSE COLLABORATION AMONG PSYCHOLOGISTS, NEUROSCIENTISTS AND THEORISTS

BY FRANCIS CRICK AND CHRISTOF KOCH

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The overwhelming question in neurobiology today is the relation between the mind and the brain. Everyone agrees that what we know as mind is closely related to certain aspects of the behavior of the brain, not to the heart, as Aristotle thought. Its most mysterious aspect is consciousness or awareness, which can take many forms, from the experience of pain to self-consciousness. In the past the mind (or soul) was often regarded, as it was by Descartes, as something immaterial, separate from the brain but interacting with it in some way. A few neuroscientists, such as the late Sir John Eccles, have asserted that the soul is distinct from the body. But most neuroscientists now believe that all aspects of mind, including its most puzzling attribute—consciousness or awareness—are likely to be explainable in a more materialistic way as the behavior of large sets of interacting neurons. As William James, the father of American psychology, said a century ago, consciousness is not a thing but a process.

Exactly what the process is, however, has yet to be discovered. For many years after James penned *The Principles of Psychology,* consciousness was a taboo concept in American psychology because of the dominance of the behaviorist movement. With the advent of cognitive science in the mid-1950s, it became possible once more for psychologists to consider mental processes as opposed to merely observing behavior. In spite of these changes, until recently most cognitive scientists ignored consciousness, as did almost all neuroscientists. The problem was felt to be either purely "philosophical" or too elusive to study experimentally. It would not have been easy for a neuroscientist to get a grant just to study consciousness.

In our opinion, such timidity is ridiculous, so some years ago we began to think about how best to attack the problem scientifically. How to explain mental events as being caused by the firing of large sets of neurons? Although there are those who believe such an approach is hopeless, we feel it is not productive to worry too much over aspects of the problem that cannot be solved scientifically or, more precisely, cannot be solved solely by using existing scientific ideas. Radically new concepts may indeed be needed—recall the modifications of scientific thinking forced on us by quantum mechanics. The only sensible approach is to press the experimental attack until we are confronted with dilemmas that call for new ways of thinking.

There are many possible approaches to the problem of consciousness. Some psychologists feel that any satisfactory theory should try to explain as many aspects of consciousness as possible, including emotion, imagination, dreams, mystical experiences and so on. Although such an all-embracing theory will be necessary in the long run, we thought it wiser to begin with the particular aspect of consciousness that is likely to yield most easily. What this aspect may be is a matter of personal judgment.

VISUAL AWARENESS primarily involves seeing what is directly in front of you, but it can be influenced by a three-dimensional representation of the object in view retained by the brain. If you see the back of a person's head, the brain infers that there is a face on the front of it. We know this is true because we would be very startled if a mirror revealed that the front was exactly like the back, as in this painting, *Reproduction Prohibited* (1937), by René Magritte.

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We selected the mammalian visual system because humans are very visual animals and because so much experimental and theoretical work has already been done on it.

It is not easy to grasp exactly what we need to explain, and it will take many careful experiments before visual consciousness can be described scientifically. We did not attempt to define consciousness itself because of the dangers of premature definition. (If this seems like a copout, try defining the word "gene"—you will not find it easy.) Yet the experimental evidence that already exists provides enough of a glimpse of the nature of visual consciousness to guide research. In this article, we will attempt to show how this evidence opens the way to attack this profound and intriguing problem.

Describing Visual Consciousness

VISUAL THEORISTS AGREE that the problem of visual consciousness is ill posed. The mathematical term "ill posed" means that additional constraints are needed to solve the problem. Although the main function of the visual system is to perceive objects and events in the world around us, the information available to our eyes is not sufficient by itself to provide the brain with its unique interpretation of the visual world. The brain must use past experience (either its own or that of our distant ancestors, which is embedded in our genes) to help interpret the information coming into our eyes. An example would be the derivation of the three-dimensional representation of the world from the two-dimensional signals falling onto the retinas of our two eyes or even onto one of them.

Visual theorists would also agree that seeing is a constructive process, one in which the brain has to carry out complex activities (sometimes called computations) in order to decide which interpretation to adopt of the ambiguous visual input. "Computation" implies that the brain acts to form a symbolic representation of the visual world, with a mapping (in the mathematical sense) of certain aspects of that world onto elements in the brain.

Ray Jackendoff of Brandeis University postulates, as do most cognitive scientists, that the computations carried out by the brain are largely unconscious and that what we become aware of is the result of these computations. But while the customary view is that this awareness occurs at the highest levels of the computational system, Jackendoff has proposed an intermediate-level theory of consciousness.

What we see, Jackendoff suggests, relates to a representation of surfaces that are directly visible to us, together with their outline, orientation, color, texture and movement. In the next stage this sketch is processed by the brain to produce a three-dimensional representation. Jackendoff argues that we are not visually aware of this three-dimensional representation.

An example may make this process clearer. If you look at a person whose back is turned to you, you can see the back of the head but not the face. Nevertheless, your brain infers that the person has a face. We can deduce as much because if that person turned around and had no face, you would be very surprised.

The viewer-centered representation that corresponds to the visible back of the head is what you are vividly aware of. What

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your brain infers about the front would come from some kind of three-dimensional representation. This does not mean that information flows only from the surface representation to the three-dimensional one; it almost certainly flows in both directions. When you imagine the front of the face, what you are aware of is a surface representation generated by information from the three-dimensional model.

It is important to distinguish between an explicit and an implicit representation. An explicit representation is something that is symbolized without further processing. An implicit representation contains the same information but requires further processing to make it explicit. The pattern of colored dots on a television screen, for example, contains an implicit representation of objects (say, a person's face), but only the dots and their locations are explicit. When you see a face on the screen, there must be neurons in your brain whose firing, in some sense, symbolizes that face.

We call this pattern of firing neurons an active representation. A latent representation of a face must also be stored in the brain, probably as a special pattern of synaptic connections between neurons. For example, you probably have a representation of the Statue of Liberty in your brain, a representation that usually is inactive. If you do think about the statue, the representation becomes active, with the relevant neurons firing away.

An object, incidentally, may be represented in more than one way—as a visual image, as a set of words and their related sounds, or even as a touch or a smell. These different representations are likely to interact with one another. The representation is likely to be distributed over many neurons, both locally and more globally. Such a representation may not be as simple and straightforward as uncritical introspection might indicate. There is suggestive evidence, partly from studying how neurons fire in various parts of a monkey's brain and partly from examining the effects of certain types of brain damage in humans, that different aspects of a face—and of the implications of a face—may be represented in different parts of the brain.

First, there is the representation of a face as a face: two eyes, a nose, a mouth and so on. The neurons involved are usually not too fussy about the exact size or position of this face in the visual field, nor are they very sensitive to small changes in its orientation. In monkeys, there are neurons that respond best when the face is turning in a particular direction, while others seem to be more concerned with the direction in which the eyes are gazing.

Then there are representations of the parts of a face, as separate from those for the face as a whole. Further, the implications of seeing a face, such as that person's sex, the facial expression, the familiarity or unfamiliarity of the face, and in particular whose face it is, may each be correlated with neurons firing in other places.

What we are aware of at any moment, in one sense or another, is not a simple matter. We have suggested that there may be a very transient form of fleeting awareness that represents only rather simple features and does not require an attentional mechanism. From this brief awareness the brain constructs a viewer-centered representation—what we see vividly and clearly—that does require attention. This in turn probably leads to three-dimensional object representations and thence to more cognitive ones.

Representations corresponding to vivid consciousness are likely to have special properties. William James thought that consciousness involved both attention and short-term memory. Most psychologists today would agree with this view. Jackendoff writes that consciousness is "enriched" by attention, implying that whereas attention may not be essential for certain limited types of consciousness, it is necessary for full consciousness. Yet it is not clear exactly which forms of memory are involved. Is long-term memory needed? Some forms of acquired knowledge are so embedded in the machinery of neural processing that they are almost certainly part of the process of becoming aware of something. On the other hand, there is evidence from studies of brain-damaged patients that the ability to lay down new long-term episodic memories is not essential for consciousness to be experienced.

It is difficult to imagine that anyone could be conscious if he or she had no memory whatsoever, even an extremely short one, of what had just happened. Visual psychologists talk of iconic memory, which lasts for a fraction of a second, and working memory (such as that used to remember a new telephone number) that lasts for only a few seconds unless it is rehearsed. It is not clear whether both of these are essential for consciousness. In any case, the division of short-term memory into these two categories may be too crude.

If these complex processes of visual awareness are localized in parts of the brain, which processes are likely to be where? Many regions of the brain may be involved, but it is almost certain that the cerebral neocortex plays a dominant role. Visual information from the retina reaches the neocortex mainly by way of a part of the thalamus (the lateral geniculate nucleus); another significant visual pathway from the retina is to the superior colliculus, at the top of the brain stem.

The cortex in humans consists of two intricately folded sheets of nerve tissue, one on each side of the head. These sheets are connected by a large tract of about 200,000 axons called the corpus callosum. It is well known that if the corpus callosum is cut in a split-brain operation, as is done for certain cases of intractable epilepsy, one side of the brain is not aware of what the other side is seeing. In particular, the left side of the brain (in a right-handed person) appears not to be aware

What we are aware of at any moment, in one sense or another, is not a simple matter.

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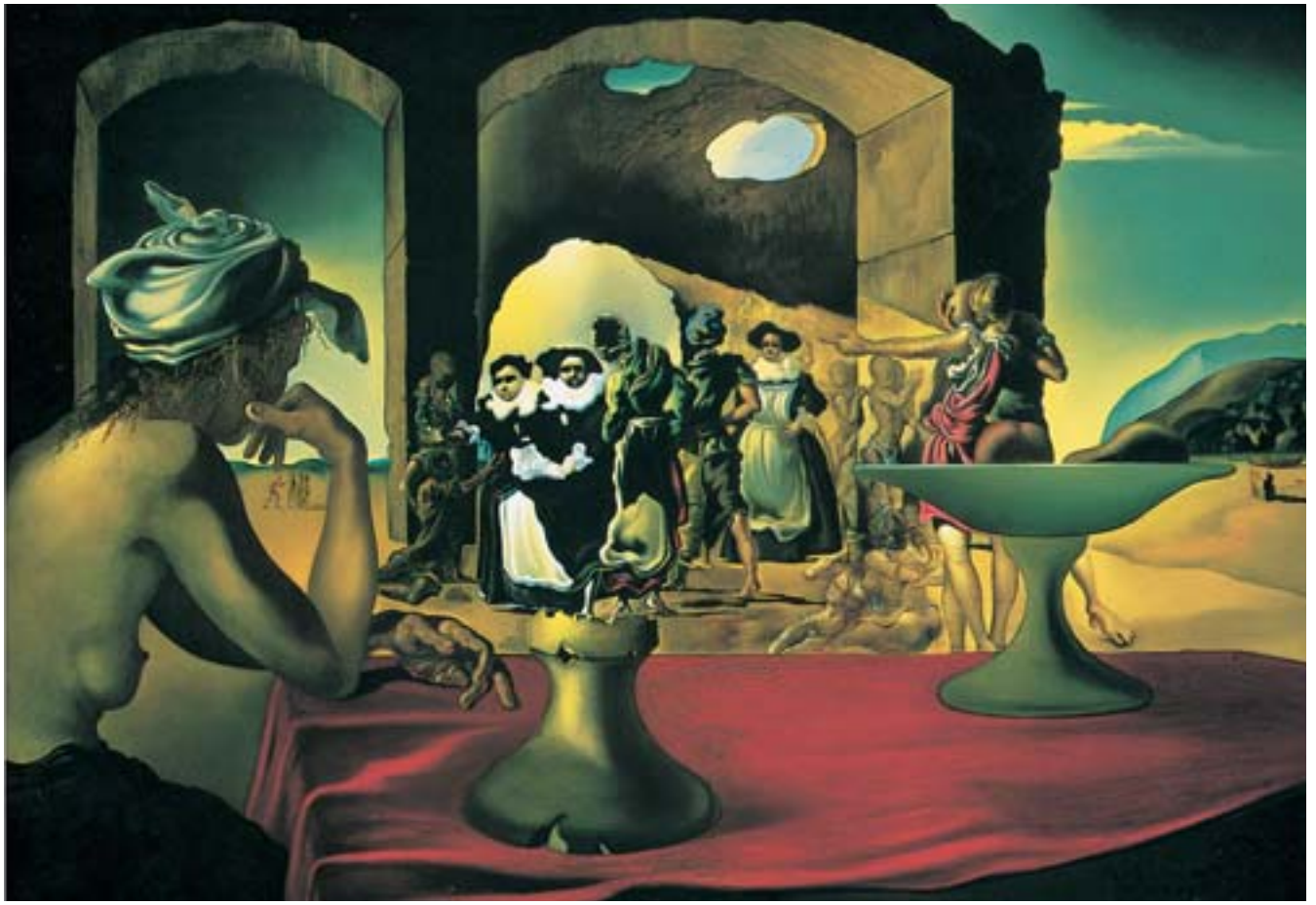

AMBIGUOUS IMAGES were frequently used by Salvador Dalí in his paintings. In *Slave Market with the Disappearing Bust of Voltaire* (1940), the head of the French philosopher Voltaire is apparent from a distance but transforms into the figures of three people when viewed at close range. Studies of monkeys shown ambiguous figures have found that many neurons in higher cortical areas respond to only the currently "perceived" figure; the neuronal response to the "unseen" image is suppressed.

of visual information received exclusively by the right side. This shows that none of the information required for visual awareness can reach the other side of the brain by traveling down to the brain stem and, from there, back up. In a normal person, such information can get to the other side only by using the axons in the corpus callosum.

A different part of the brain—the hippocampal system—is involved in one-shot, or episodic, memories that, over weeks and months, it passes on to the neocortex. This system is so placed that it receives inputs from, and projects to, many parts of the brain. Thus, one might suspect that the hippocampal system is the essential seat of consciousness. This is not the case: evidence from studies of patients with damaged brains shows that this system is not essential for visual awareness, although naturally a patient lacking one is severely handicapped in everyday life because he cannot remember anything that took place more than a minute or so in the past.

In broad terms, the neocortex of alert animals probably acts in two ways. By building on crude and somewhat redundant wiring, produced by our genes and by embryonic processes, the neocortex draws on visual and other experience to slowly "rewire" itself to create categories (or "features") it can respond to. A new category is not fully created in the neocortex after exposure to only one example of it, although some small modifications of the neural connections may be made.

The second function of the neocortex (at least of the visual part of it) is to respond extremely rapidly to incoming signals. To do so, it uses the categories it has learned and tries to find the combinations of active neurons that, on the basis of its past experience, are most likely to represent the relevant objects and events in

THE AUTHORS

FRANCIS CRICK and *CHRISTOF KOCH* share an interest in the experimental study of consciousness. Crick is the co-discoverer, with James Watson, of the double helical structure of DNA. While at the Medical Research Council Laboratory of Molecular Biology in Cambridge, England, he worked on the genetic code and on developmental biology. Since 1976 he has been at the Salk Institute for Biological Studies in San Diego. His main interest lies in understanding the visual system of mammals. Koch was awarded his Ph.D. in biophysics by the University of Tübingen in Germany. After a stint at M.I.T., he joined the California Institute of Technology, where he is Lois and Victor Troendle Professor of Cognitive and Behavioral Biology. He studies how single brain cells process information and the neural basis of motion perception, visual attention, and awareness in mice, monkeys and humans.

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the visual world at that moment. The formation of such coalitions of active neurons may also be influenced by biases coming from other parts of the brain: for example, signals telling it what best to attend to or high-level expectations about the nature of the stimulus.

Consciousness, as James noted, is always changing. These rapidly formed coalitions occur at different levels and interact to form even broader coalitions. They are transient, lasting usually for only a fraction of a second. Because coalitions in the visual system are the basis of what we see, evolution has seen to it that they form as fast as possible; otherwise, no animal could survive. The brain is handicapped in forming neuronal coalitions rapidly because, by computer standards, neurons act very slowly. The brain compensates for this relative slowness partly by using very many neurons, simultaneously and in parallel, and partly by arranging the system in a roughly hierarchical manner.

If visual awareness at any moment corresponds to sets of neurons firing, then the obvious question is: Where are these neurons located in the brain, and in what way are they firing? Visual awareness is highly unlikely to occupy all the neurons in the neocortex that are firing above their background rate at a particular moment. We would expect that, theoretically, at least some of these neurons would be involved in doing computations—trying to arrive at the best coalitions—whereas others would express the results of these computations, in other words, what we see.

Fortunately, some experimental evidence can be found to back up this theoretical conclusion. A phenomenon called binocular rivalry may help identify the neurons whose firing symbolizes awareness. This phenomenon can be seen in dramatic form in an exhibit prepared by Sally Duensing and Bob Miller at the Exploratorium in San Francisco.

Binocular rivalry occurs when each eye has a different visual input relating to the same part of the visual field. The early visual system on the left side of the brain receives an input from both eyes but sees only the part of the visual field to the right of the fixation point. The converse is true for the right side. If these two conflicting inputs are rivalrous, one sees not the two inputs superimposed but first one input, then the other, and so on in alternation.

In the exhibit, called "The Cheshire Cat," viewers put their heads in a fixed place and are told to keep the gaze fixed. By means of a suitably placed mirror, one of the eyes can look at another person's face, directly in front, while the other eye sees a blank white screen to the side. If the viewer waves a hand in front of this plain screen at the same location in his or her visual field occupied by the face, the face is wiped out. The movement of the hand, being visually very salient, has captured the brain's attention. Without attention the face cannot be seen. If the viewer moves the eyes, the face reappears.

In some cases, only part of the face disappears. Sometimes, for example, one eye, or both eyes, will remain. If the viewer looks at the smile on the person's face, the face may disappear, leaving only the smile. For this reason, the effect has been called the Cheshire Cat effect, after the cat in Lewis Carroll's *Alice's Adventures in Wonderland*.

Although it is difficult, though not impossible, to record activity in individual neurons in a human brain, such studies can be done in monkeys. A simple example of binocular rivalry was studied in a monkey by Nikos K. Logothetis and Jeffrey D. Schall, both then at M.I.T. They trained a macaque to keep its eyes still and to signal whether it is seeing upward or downward movement of a horizontal grating. To produce rivalry, upward movement is projected into one of the monkey's eyes and downward movement into the other, so that the two images overlap in the visual field. The monkey signals that it sees up and down movements alternatively, just as humans would. Even though the motion stimulus coming into the monkey's eyes is always the same, the monkey's percept changes every second or so.

Cortical area MT (which some researchers prefer to label V5) is an area mainly concerned with movement. What do the neurons in area MT do when the monkey's percept is sometimes up and sometimes down? (The researchers studied only the monkey's first response.) The simplified answer—the actual data are rather more messy—is that whereas the firing of some of the neurons correlates with the changes in the percept, for others the average firing rate is relatively unchanged and independent of which direction of movement the monkey is seeing at that moment. Thus, it is unlikely that the firing of all the neurons in the visual neocortex at one particular moment corresponds to the monkey's visual awareness. Exactly which neurons do correspond to awareness remains to be discovered.

When we clearly see something, there must be neurons actively firing that stand for what we see.

We have postulated that when we clearly see something, there must be neurons actively firing that stand for what we see. This might be called the activity principle. Here, too, there is some experimental evidence. One example is the firing of neurons in a specific cortical visual area in response to illusory contours. Another and perhaps more striking case is the filling in of the blind spot. The blind spot in each eye is caused by the lack of photoreceptors in the area of the retina where the optic nerve leaves the retina and projects to the brain. Its location is about 15 degrees from the fovea (the visual center of the eye). Yet if you close one eye, you do not see a hole in your visual field.

Philosopher Daniel C. Dennett of Tufts University is unusual among philosophers in that he is interested both in psychology and in the brain. This interest is to be welcomed. In his 1991 book, *Consciousness Explained*, he argues that it is wrong to talk about filling in. He concludes, correctly, that "an absence of information is not the same as information

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about an absence." From this general principle he argues that the brain does not fill in the blind spot but rather ignores it.

Dennett's argument by itself, however, does not establish that filling in does not occur; it only suggests that it might not. Dennett also states that "your brain has no machinery for [filling in] at this location." This statement is incorrect. The primary visual cortex lacks a direct input from one eye, but normal "machinery" is there to deal with the input from the other eye. Ricardo Gattass and his colleagues at the Federal University of Rio de Janeiro have shown that in the macaque some of the neurons in the blind-spot area of the primary visual cortex do respond to input from both eyes, probably assisted by inputs from other parts of the cortex. Moreover, in the case of simple filling in, some of the neurons in that region respond as if they were actively filling in.

Thus, Dennett's claim about blind spots is incorrect. In addition, psychological experiments by Vilayanur S. Ramachandran [see "Blind Spots," Scientific American, May 1992] have shown that what is filled in can be quite complex depending on the overall context of the visual scene. How, he argues, can your brain be ignoring something that is in fact commanding attention?

Filling in, therefore, is not to be dismissed as nonexistent or unusual. It probably represents a basic interpolation process that can occur at many levels in the neocortex. It is a good example of what is meant by a constructive process.

How can we discover the neurons whose firing symbolizes a particular percept? William T. Newsome and his colleagues at Stanford University did a series of brilliant experiments on neurons in cortical area MT of the macaque's brain. By studying a neuron in area MT, we may discover that it responds best to very specific visual features having to do with motion. A neuron, for instance, might fire strongly in response to the movement of a bar in a particular place in the visual field, but only when the bar is oriented at a certain angle, moving in one of the two directions perpendicular to its length within a certain range of speed.

It is technically difficult to excite just a single neuron, but it is known that neurons that respond to roughly the same position, orientation and direction of movement of a bar tend to be located near one another in the cortical sheet. The experimenters taught the monkey a simple task in movement discrimination using a mixture of dots, some moving randomly, the rest all in one direction. They showed that electrical stimulation of a small region in the right place in cortical area MT would bias the monkey's motion discrimination, almost always in the expected direction.

KNOWLEDGE about visual systems is important in the study of consciousness.

Thus, the stimulation of these neurons can influence the monkey's behavior and probably its visual percept. Such experiments do not, however, show decisively that the firing of such neurons is the exact neural correlate of the percept. The correlate could be only a subset of the neurons being activated. Or perhaps the real correlate is the firing of neurons in another part of the visual hierarchy that are strongly influenced by the neurons activated in area MT.

These same reservations also apply to cases of binocular rivalry. Clearly, the problem of finding the neurons whose firing symbolizes a particular percept is not going to be easy. It will take many careful experiments to track them down even for one kind of percept.

Visual Awareness

IT SEEMS OBVIOUS that the purpose of vivid visual awareness is to feed into the cortical areas concerned with the implications of what we see; from there the information shuttles on the one hand to the hippocampal system, to be encoded (temporarily) into long-term episodic memory, and on the other to the planning levels of the motor system. But is it possible to go from a visual input to a behavioral output without any relevant visual awareness?

That such a process can happen is demonstrated by a very small and remarkable class of patients with "blindsight." These patients, all of whom have suffered damage to their visual cortex, can point with fair accuracy at visual targets or track them with their eyes while vigorously denying seeing anything. In fact, these patients are as surprised as their doctors by their abilities. The amount of information that "gets through," however, is limited: blindsight patients have some ability to respond to wavelength, orientation and motion, yet they cannot distinguish a triangle from a square.

It is of great interest to know which neural pathways are being used in these patients. Investigators originally suspected that the pathway ran through the superior colliculus. Subsequent experiments suggested that a direct, albeit weak, connection may be involved between the lateral geniculate nucleus and other visual areas in the cortex. It is unclear whether an intact primary visual cortex region is essential for immediate visual awareness. Conceivably the visual signal in blindsight is so weak that the neural activity cannot produce awareness, although it remains strong enough to get through to the motor system.

Normal-seeing people regularly respond to visual signals without being fully aware of them. In automatic actions, such as swimming or driving a car, complex but stereotypical actions occur with little, if any, associated visual awareness. In other cases, the information conveyed is either very limited or very attenuated.

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Thus, while we can function without visual awareness, our behavior without it is rather restricted.

Clearly, it takes a certain amount of time to experience a conscious percept. It is difficult to determine just how much time is needed for an episode of visual awareness, but one aspect of the problem that can be demonstrated experimentally is that signals that are received close together in time are treated by the brain as simultaneous.

A disk of red light is flashed for, say, 20 milliseconds, followed immediately by a 20-millisecond flash of green light in the same place. The subject reports that he did not see a red light followed by a green light. Instead he saw a yellow light, just as he would have if the red and the green light had been flashed simultaneously. Yet the subject could not have experienced yellow until after the information from the green flash had been processed and integrated with the preceding red one.

Experiments of this type led psychologist Robert Efron of the University of California at Davis to conclude that the processing period for perception is about 60 to 70 milliseconds. Similar periods are found in experiments with tones in the auditory system. It is always possible, however, that the processing times may be different in higher parts of the visual hierarchy and in other parts of the brain. Processing is also more rapid in trained, compared with naive, observers.

Because attention appears to be involved in some forms of visual awareness, it would help if we could discover its neural basis. Eye movement is a form of attention, since the area of the visual field in which we see with high resolution is remarkably small, roughly the area of the thumbnail at arm's length. Thus, we move our eyes to gaze directly at an object in order to see it more clearly. Our eyes usually move three or four times a second. Psychologists have shown, however, that there appears to be a faster form of attention that moves around, in some sense, when our eyes are stationary.

The exact psychological nature of this faster attentional mechanism is controversial. Several neuroscientists, however, including Robert Desimone and his colleagues at the National Institute of Mental Health, have shown that the rate of firing of certain neurons in the macaque's visual system depends on what the monkey is attending to in the visual field. Thus, attention is not solely a psychological concept; it also has neural correlates that can be observed. A number of researchers have found that the pulvinar, a region of the thalamus, appears to be involved in visual attention. We would like to believe that the thalamus deserves to be called "the organ of attention," but this status has yet to be established.

Attention and Awareness

THE MAJOR PROBLEM is to find what activity in the brain corresponds directly to visual awareness. It has been speculated that each cortical area produces awareness of only those visual features that are "columnar," or arranged in the stack or column of neurons perpendicular to the cortical surface. Thus, the primary visual cortex could code for orientation and area MT for certain aspects of motion. So far experimentalists have not found one region in the brain where all the information needed for visual awareness appears to come together. Dennett has dubbed such a hypothetical place "The Cartesian Theater." He argues on theoretical grounds that it does not exist.

Awareness seems to be distributed not just on a local scale but more widely over the neocortex. Vivid visual awareness is unlikely to be distributed over every cortical area, because some areas show no response to visual signals. Awareness might, for example, be associated with only those areas that connect back directly to the primary visual cortex or alternatively with those areas that project into one another's layer 4. (The latter areas are always at the same level in the visual hierarchy.)

The key issue, then, is how the brain forms its global representations from visual signals. If attention is indeed crucial for visual awareness, the brain could form representations by attending to just one object at a time, rapidly moving from one object to the next. For example, the neurons representing all the different aspects of the attended object could all fire together very rapidly for a short period, possibly in rapid bursts.

This fast, simultaneous firing might not only excite those neurons that symbolized the implications of that object but also temporarily strengthen the relevant synapses so that this particular pattern of firing could be quickly recalled—a form of short-term memory. If only one representation needs to be held in short-term memory, as in remembering a single task, the neurons involved may continue to fire for a period.

The key issue is how the brain forms its global representations from visual signals.

A problem arises if it is necessary to be aware of more than one object at exactly the same time. If all the attributes of two or more objects were represented by neurons firing rapidly, their attributes might be confused. The color of one might become attached to the shape of another. This happens sometimes in very brief presentations.

Some time ago Christoph von der Malsburg, now at Ruhr University Bochum in Germany, suggested that this difficulty would be circumvented if the neurons associated with any one object all fired in synchrony (that is, if their times of firing were correlated) but were out of synchrony with those representing other objects. Two other groups in Germany reported that there does appear to be correlated firing between neurons in the visual cortex of the cat, often in a rhythmic manner, with a frequency in the 35- to 75-hertz range, sometimes called 40-hertz, or γ, oscillation.

Von der Malsburg's proposal prompt-

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ed us to suggest that this rhythmic and synchronized firing might be the neural correlate of awareness and that it might serve to bind together activity concerning the same object in different cortical areas. The matter is still undecided, but at present the fragmentary experimental evidence does rather little to support such an idea. Another possibility is that the 40-hertz oscillations may help distinguish figure from ground or assist the mechanism of attention.

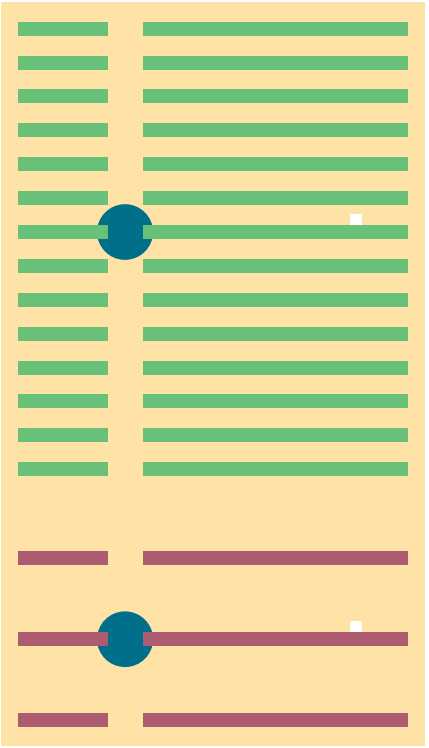
Correlates of Consciousness

ARE THERE SOME particular types of neurons, distributed over the visual neocortex, whose firing directly symbolizes the content of visual awareness? One very simplistic hypothesis is that the activities in the upper layers of the cortex are largely unconscious ones, whereas the activities in the lower layers (layers 5 and 6) mostly correlate with consciousness. We have wondered whether the pyramidal neurons in layer 5 of the neocortex, especially the larger ones, might play this latter role.

These are the only cortical neurons that project right out of the cortical system (that is, not to the neocortex, the thalamus or the claustrum). If visual awareness represents the results of neural computations in the cortex, one might expect that what the cortex sends elsewhere would symbolize those results. Moreover, the neurons in layer 5 show a rather unusual propensity to fire in bursts. The idea that layer 5 neurons may directly symbolize visual awareness is attractive, but it still is too early to tell whether there is anything in it.

Visual awareness is clearly a difficult problem. More work is needed on the psychological and neural basis of both attention and very short term memory. Studying the neurons when a percept changes, even though the visual input is constant, should be a powerful experimental paradigm. We need to construct neurobiological theories of visual awareness and test them using a combination of molecular, neurobiological and clinical imaging studies.

We believe that once we have mastered the secret of this simple form of awareness, we may be close to understanding a central mystery of human life: how the physical events occurring in our brains while we think and act in the world relate to our subjective sensations—that is, how the brain relates to the mind.



OPTICAL ILLUSION devised by Vilayanur S. Ramachandran illustrates the brain's ability to reconstruct missing visual information that falls on the blind spot of the eye. When you look at the patterns of broken green bars, the visual system produces two illusory contours defining a vertical strip. Now shut your right eye and focus on the white square in the green series of bars. Move the page toward the eye until the dot disappears (roughly six inches away). Most people see the vertical strip completed across the blind spot, not the broken line. Try the same experiment with the series of three red bars. The illusory vertical contours are less well defined, and the visual system tends to fill in the horizontal bar across the blind spot. Thus, the brain fills in differently depending on the image.

Postscript

THERE HAVE BEEN several relevant developments since this article was first published in 1992. It now seems likely that there are rapid "online" systems for stereotyped motor responses such as hand and eye movement. These systems are unconscious and lack memory. Conscious seeing, on the other hand, seems to be slower and more subject to visual illusions. The brain needs to form a conscious representation of the visual scene that it can then employ for many different actions or thoughts.

Why is consciousness needed? Why could our brains not consist of a whole series of stereotyped online systems? We would argue that far too many would be required to express human behavior. The slower, conscious mode allows time for the individual neurons to become sensitive to the context of what typically excites them, so that a broader view of the current state of affairs can be constructed. It would be a great evolutionary advantage to be able to respond very rapidly to stereotyped situations and also, more slowly, to more complex and novel ones. Usually both these modes will act in parallel. Exactly how all these pathways work and how they interact are far from clear.

There have been more experiments on the behavior of neurons that respond to bistable visual percepts, such as binocular rivalry, but it is probably too early to draw firm conclusions from them about the exact neural correlates of visual consciousness. We have suggested on theoretical grounds based on the neuroanatomy of the macaque that primates are not directly aware of what is happening in the primary visual cortex, even though most of the visual information flows through it. This hypothesis is supported by some experimental evidence, but it is still controversial. SA

MORE TO EXPLORE

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IN THEIR SEARCH FOR THE MIND, SCIENTISTS ARE FOCUSING ON VISUAL PERCEPTION—HOW WE INTERPRET WHAT WE SEE

vision: a window on consciousness

BY NIKOS K. LOGOTHETIS

WHEN YOU first look at the center image in the painting by Salvador Dalí reproduced at the right, what do you see? Most people immediately perceive a man's face, eyes gazing skyward and lips pursed under a bushy mustache. But when you look again, the image rearranges itself into a more complex tableau. The man's nose and white mustache become the mobcap and cape of a seated woman. The glimmers in the man's eyes reveal themselves as lights in the windows—or glints on the roofs—of two cottages nestled in darkened hillsides. Shadows on the man's cheek emerge as a child in short pants standing beside the seated woman—both of whom, it is now clear, are looking across a lake at the cottages from a hole in a brick wall, a hole that we once saw as the outline of the man's face.

In 1940, when he rendered *Old Age, Adolescence, Infancy (The Three Ages)*—which contains three "faces"—Dalí was toying with the capacity of the viewer's mind to interpret two different images from the same set of brushstrokes. More than 50 years later, researchers, including my colleagues and me, are using similarly ambiguous visual stimuli to try to identify the brain activity that underlies consciousness. Specifically, we want to know what happens in the brain at the instant when, for example, an observer comprehends that the three faces in Dalí's picture are not really faces at all.

Consciousness is a difficult concept to define, much less to study. Neuroscientists have in recent years made impressive progress toward understanding the complex patterns of activity that occur in nerve cells, or neurons, in the brain. Even so, most people, including many scientists, still find the notion that electrochemical discharges in neurons can explain the mind—and in particular consciousness—challenging.

Yet, as Nobel laureate Francis Crick of the Salk Institute for Biological Studies in San Diego and Christof Koch of the California Institute of Technology have argued, the problem of consciousness can be broken down into several separate questions, some of which can be subjected to scientific inquiry [see "The Problem of Consciousness," by Francis Crick and Christof Koch, on page 10]. For example, rather than worrying about what consciousness is, one can ask: What is the difference between the neural processes that correlate with a particular conscious experience and those that do not?

Updated from the November 1999 issue
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Now You See It ...

THAT IS WHERE AMBIGUOUS stimuli come in. Perceptual ambiguity is not a whimsical behavior specific to the organization of the visual system. Rather it tells us something about the organization of the entire brain and its way of making us aware of all sensory information. Take, for instance, the meaningless string of French words *pas de lieu Rhône que nous,* cited by the psychologist William James in 1890. You can read this over and over again without recognizing that it sounds just like the phrase "paddle your own canoe." What changes in neural activity occur when the meaningful sentence suddenly reaches consciousness?

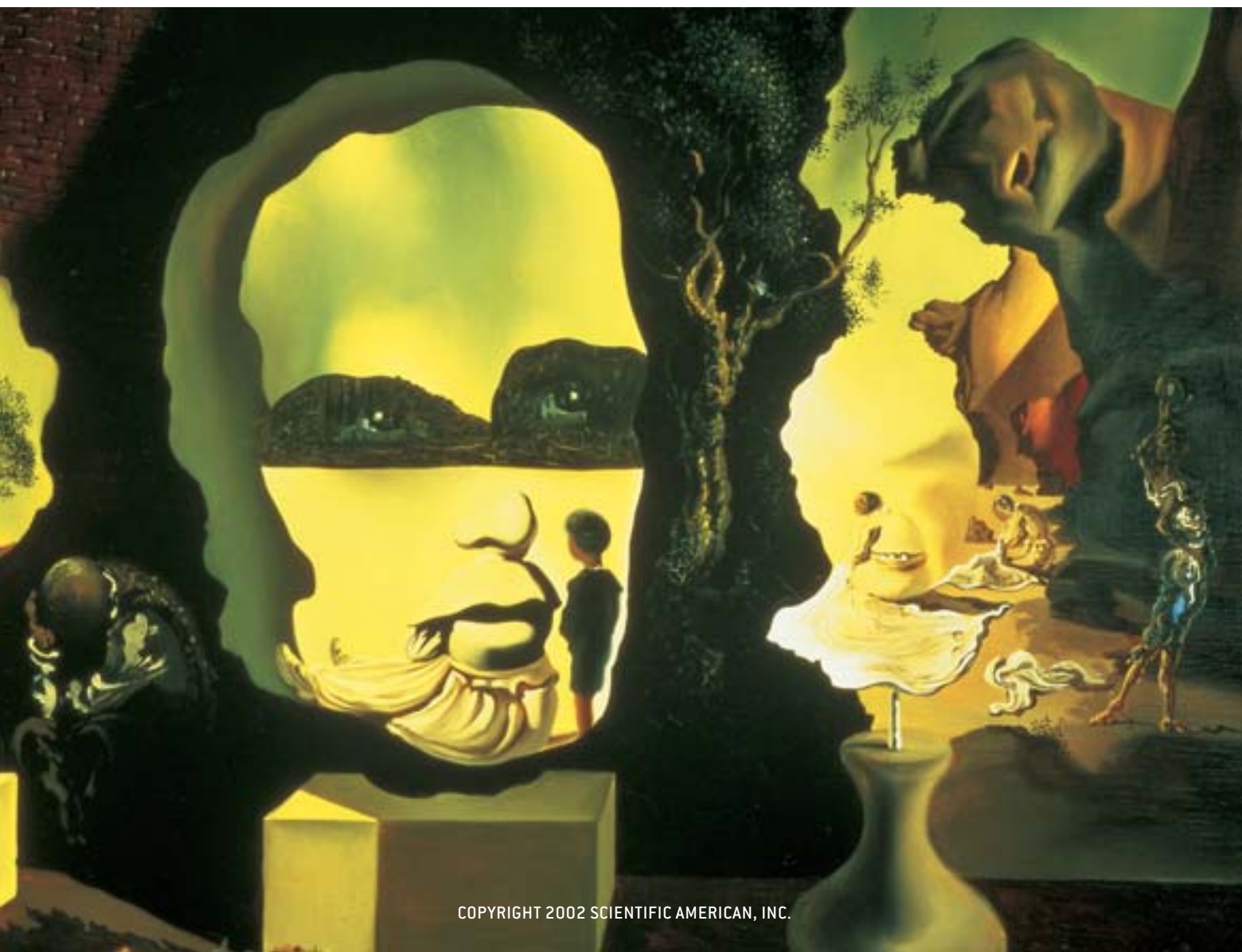
In our work with ambiguous visual stimuli, we use images that not only give rise to two distinct perceptions but also instigate a continuous alternation between the two. A familiar example is the Necker cube [*see illustration on next page*]. This figure is perceived as a three-dimensional cube, but the apparent perspective of the cube appears to shift every few seconds. Obviously, this alternation must correspond to something happening in the brain.

A skeptic might argue that we sometimes perceive a stimulus without being truly conscious of it, as when, for example, we "automatically" stop at a red light when driving. But the stimuli and the situations that I investigate are actually designed to reach consciousness.

We know that our stimuli reach awareness in human beings, because they can tell us about their experience. But it is not usually possible to study the activity of individual neurons in awake humans, so we perform our experiments with alert monkeys that have been trained to report what they are perceiving by pressing levers or by looking in a particular direction. Monkeys' brains are organized like those of humans, and they respond to such stimuli much as humans do. Consequently, we think the animals are conscious in somewhat the same way as humans are.

We investigate ambiguities that result when two different visual patterns are presented simultaneously to each eye, a phe-

AMBIGUOUS STIMULI, such as this painting by Salvador Dalí, entitled *Old Age, Adolescence, Infancy (The Three Ages)*, aid scientists who use visual perception to study the phenomenon of consciousness.



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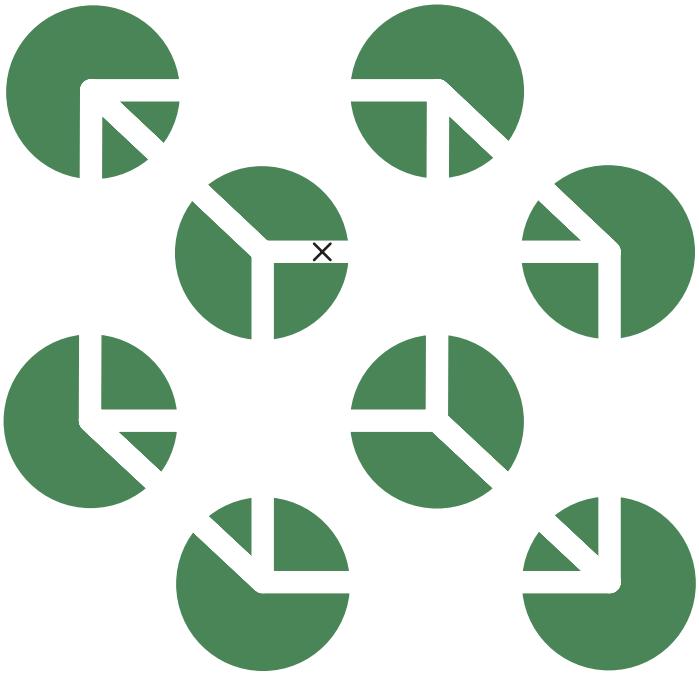

NECKER CUBE can be viewed two different ways, depending on whether you see the "x" on the top front edge of the cube or on its rear face. Sometimes the cube appears superimposed on the circles; other times it seems as if the circles are holes and the cube is floating behind the page.

nomenon called binocular rivalry. When people are put in this situation, their brains become aware first of one perception and then the other, in a slowly alternating sequence [*see box on opposite page*].

In the laboratory, we use stereoscopes to create this effect. Trained monkeys exposed to such visual stimulation report that they, too, experience a perception that changes every few seconds. Our experiments have enabled us to trace neural activity that corresponds to these changing reports.

In the Mind's Eye

STUDIES OF NEURAL ACTIVITY in animals conducted over several decades have established that visual information leaving the eyes ascends through successive stages of a neural data-processing system. Different modules analyze various attributes of the visual field. In general, the type of processing becomes more specialized the farther the information moves along the visual pathway [*see illustration on page 22*].

At the start of the pathway, images from the retina at the back of each eye are channeled first to a pair of small structures deep in the brain called the lateral geniculate nuclei (LGN). Individual neurons in the LGN can be activated by visual stimulation from either one eye or the other but not both. They respond to any change of brightness or color in a specific region within an area of view known as the receptive field, which varies among neurons.

From the LGN, visual information moves to the primary visual cortex, known as V1, which is at the back of the head. Neurons in V1 behave differently than those in the LGN do. They can usually be activated by either eye, but they are also sensitive to specific attributes, such as the direction of motion of a stimulus placed within their receptive field. Visual information is transmitted from V1 to more than two dozen other distinct cortical regions.

Some information from V1 can be traced as it moves through areas known as V2 and V4 before winding up in regions known as the inferior temporal cortex (ITC), which like all the other structures are bilateral. A large number of investigations, including neurological studies of people who have experienced brain damage, suggest that the ITC is important in perceiving form and recognizing objects. Neurons in V4 are known to respond selectively to aspects of visual stimuli critical to discerning shapes. In the ITC, some neurons behave like V4 cells, but others respond only when entire objects, such as faces, are placed within their very large receptive fields.

Other signals from V1 pass through regions V2, V3 and an area known as MT/V5 before eventually reaching a part of the brain called the parietal lobe. Most neurons in MT/V5 respond strongly to items moving in a specific direction. Neurons in other areas of the parietal lobe respond when an animal pays attention to a stimulus or intends to move toward it.

One surprising observation made in early experiments is that many neurons in these visual pathways, both in V1 and in higher levels of the processing hierarchy, still respond with their characteristic selectivity to visual stimuli even in animals that have been completely anesthetized. Clearly, an animal (or a human) is not conscious of all neural activity.

The observation raises the question of whether awareness is the result of the activation of special brain regions or clusters of neurons. The study of binocular rivalry in alert, trained monkeys allows us to approach that question, at least to some extent. In such experiments, a re-

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searcher presents each animal with a variety of visual stimuli, usually patterns or figures projected onto a screen. Monkeys can easily be trained to report accurately what stimulus they perceive by means of rewards of fruit juice [*see box on pages 24 and 25*].

During the experiment, the scientist uses electrodes to record the activity of neurons in the visual-processing pathway. Neurons vary markedly in their responsiveness when identical stimuli are presented to both eyes simultaneously. Stimulus pattern A might provoke activity in one neuron, for instance, whereas stimulus pattern B does not.

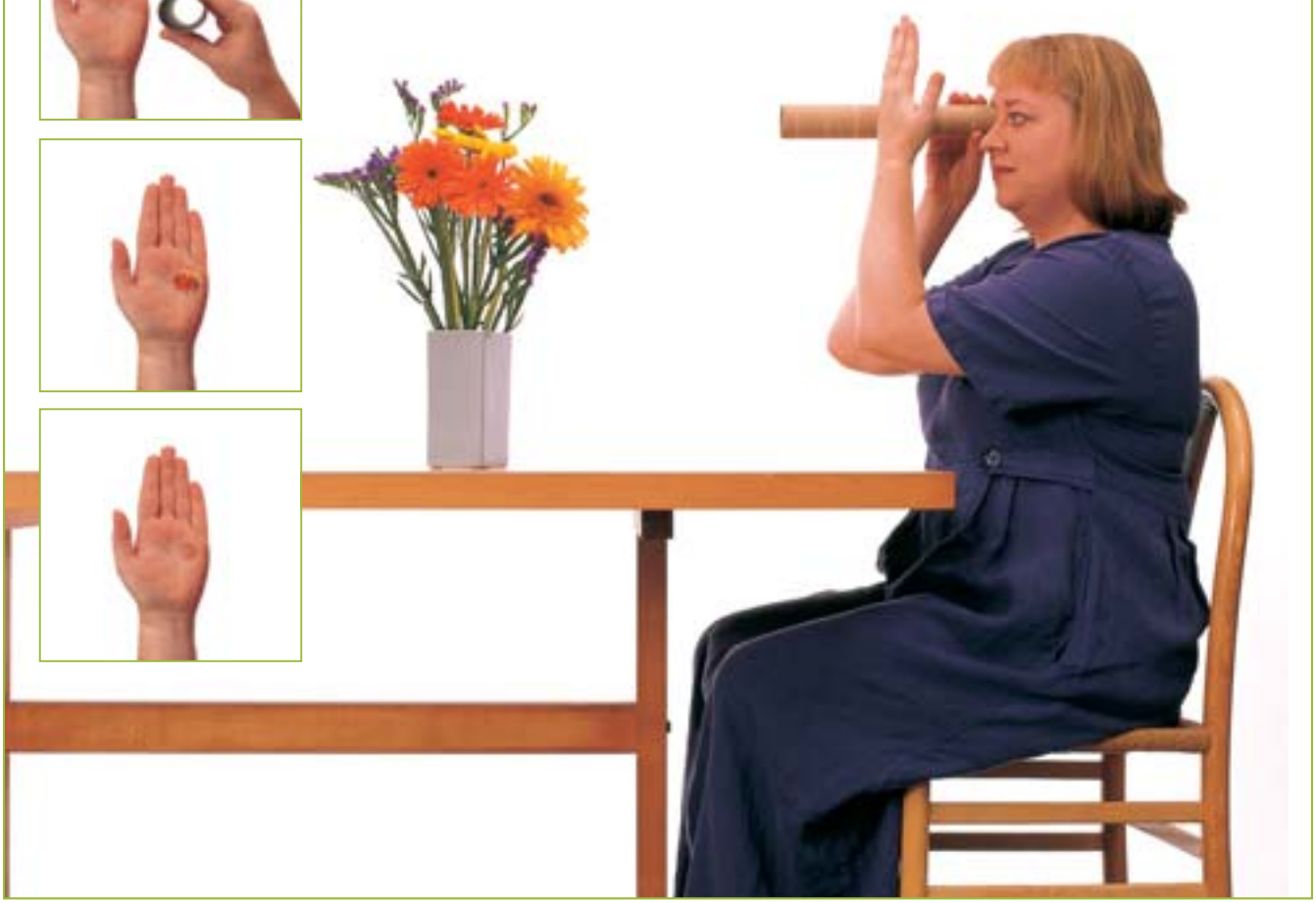
Once an experimenter has identified an effective and an ineffective stimulus for a given neuron (by presenting the same stimulus to both eyes at once), the two stimuli can be presented so that a different one is seen by each eye. We expect that, like a human in this situation, the monkey will become aware of the two stimuli in an alternating sequence. And, indeed, that is what the monkeys tell us by their responses when we present them

HOW TO EXPERIENCE BINOCULAR RIVALRY

To simulate binocular rivalry at home, use your right hand to hold the cardboard cylinder from a roll of paper towels (or a piece of paper rolled into a tube) against your right eye. Hold your left hand, palm facing you, roughly four inches in front of your left eye, with the edge of your hand touching the tube.

At first it will appear as though your hand has a hole in it, as your brain concentrates on the stimulus from your right eye. After a few seconds, though, the "hole" will fill in with a fuzzy perception of your whole palm from your left eye. If you keep looking, the two images will alternate, as your brain selects first the visual stimulus viewed by one eye, then that viewed by the other. The alternation is, however, a bit biased; you will probably perceive the visual stimulus you see through the cylinder more frequently than you will see your palm.

The bias occurs for two reasons. First, your palm is out of focus because it is much closer to your face, and blurred visual stimuli tend to be weaker competitors in binocular rivalry than sharp patterns, such as the surroundings you are viewing through the tube. Second, your palm is a relatively smooth surface with less contrast and fewer contours than your comparatively rich environment. In the laboratory, we carefully select the patterns viewed by the subjects to eliminate such bias. —*N.K.L.*



DAN WAGNER

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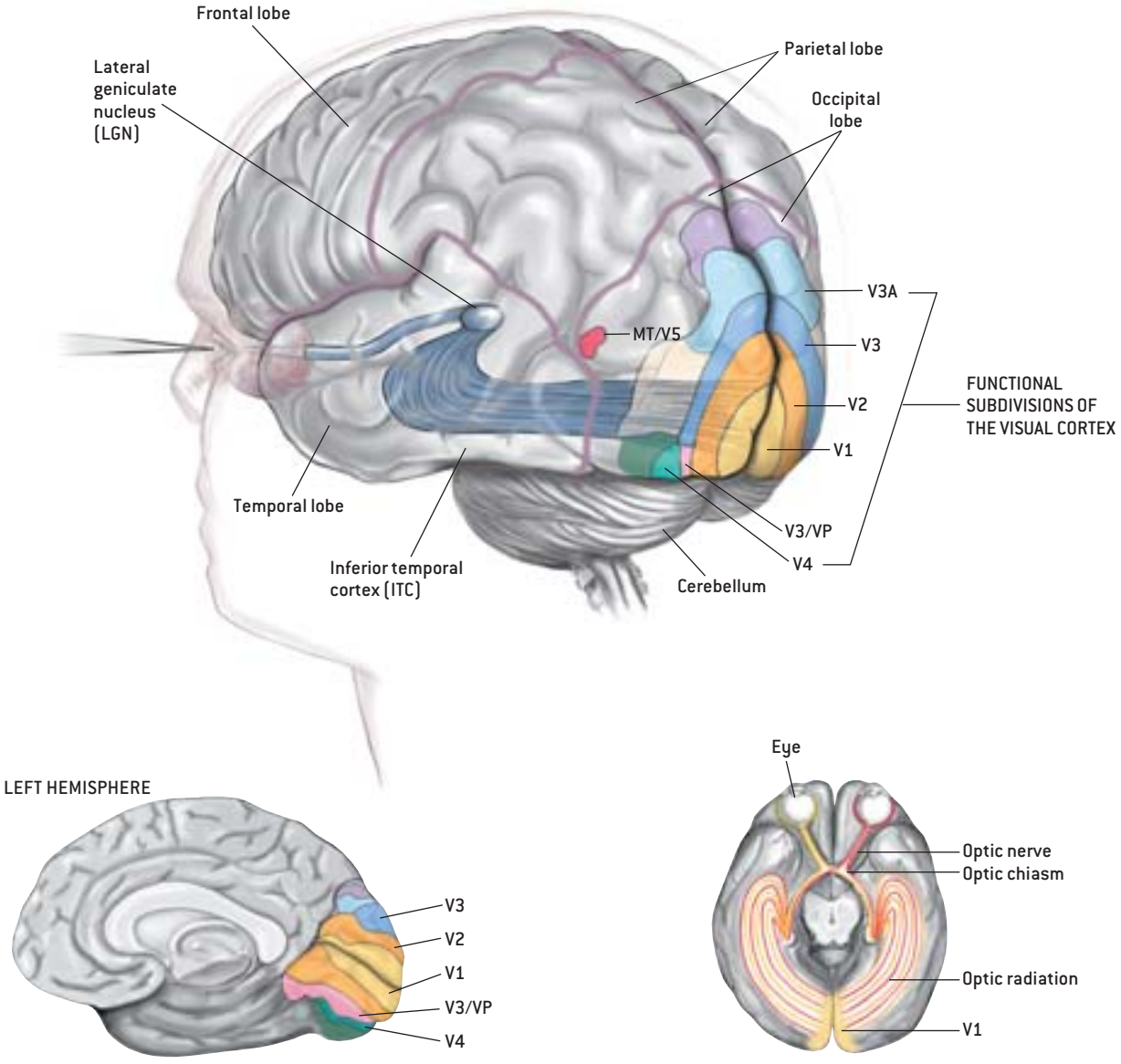
with such rivalrous pairs of stimuli. By recording from neurons during successive presentations of rivalrous pairs, an experimenter can evaluate which neurons change their activity only when the stimuli change and which neurons alter their rate of firing when the animal reports a changed perception that is not accompanied by a change in the stimuli.

Jeffrey D. Schall, now at Vanderbilt University, and I carried out a version of this experiment in which one eye saw a grating that drifted slowly upward while the other eye saw a downward-moving grating. We recorded from visual area MT/V5, where cells tend to be responsive to motion. We found that about 43 percent of the cells in this area changed their level of activity when the monkey indicated that its perception had changed from up to down, or vice versa. Most of these cells were in the deepest layers of MT/V5.

The percentage we measured was actually a lower proportion than most scientists would have guessed, because almost all neurons in MT/V5 are sensitive to direction of movement. The majority of neurons in MT/V5 did behave somewhat like those in V1, remaining active when their preferred stimulus was in view of either eye, whether it was being perceived or not.

There were further surprises. Some 11 percent of the neurons examined were excited when the monkey reported perceiving the more effective stimulus of an upward/downward pair for the neuron in question. But, paradoxically, a similar proportion of neurons was most excited when the most effective stimulus was not perceived—even though it was in clear view of one eye. Other neurons could not



HUMAN VISUAL PATHWAY begins with the eyes and extends through several interior brain structures before ascending to the various regions of the visual cortex (V1, and so on). At the optic chiasm, the optic nerves cross over partially so that each hemisphere of the brain receives input from both eyes. The information is filtered by the lateral geniculate nucleus, which consists of layers of nerve cells that each respond only to stimuli from one eye. The inferior temporal cortex is important for seeing forms. Some cells from each area are active only when a person or monkey becomes conscious of a given stimulus.

TERESE WINSLOW, WITH ASSISTANCE FROM HEIDI BASELER, BILL PRESS AND BRIAN WANDELL *Stanford University*

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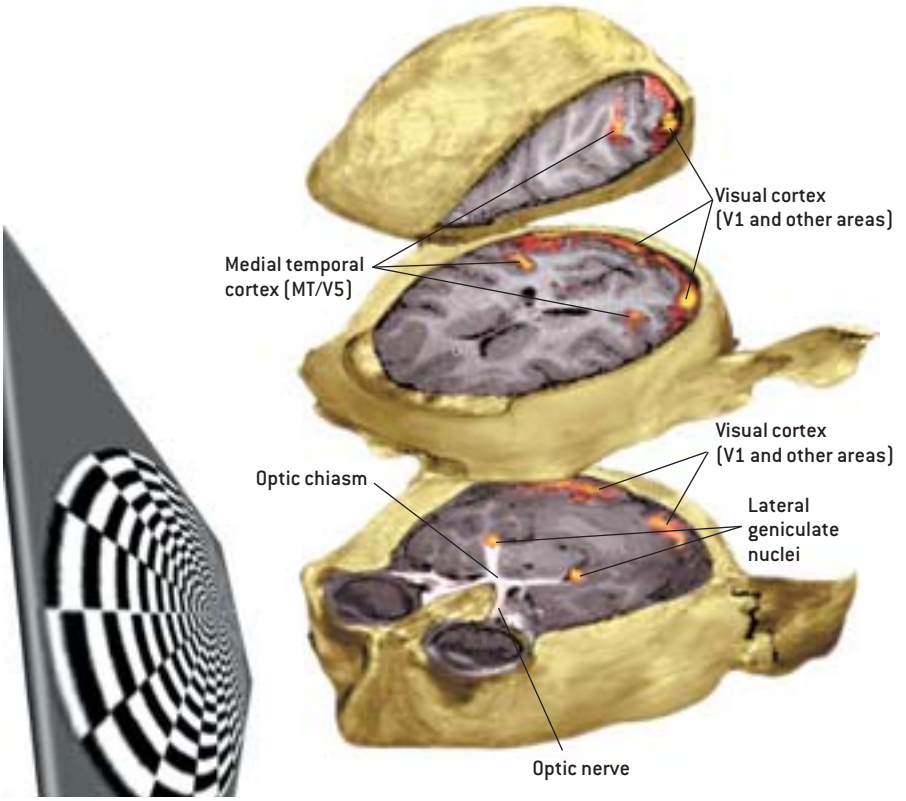
be categorized as preferring one stimulus over another.

While we were both at Baylor College of Medicine, David A. Leopold and I studied neurons in parts of the brain known to be important in recognizing objects. (Leopold is now with me at the Max Planck Institute for Biological Cybernetics in Tübingen, Germany.) We recorded activity in V4, as well as in V1 and V2, while animals viewed stimuli consisting of lines sloping either to the left or to the right. In V4 the proportion of cells whose activity reflected perception was similar to that which Schall and I had found in MT/V5, around 40 percent. But again, a substantial proportion fired best when their preferred stimulus was not perceived. In V1 and V2, in contrast, fewer than one in 10 of the cells fired exclusively when their more effective stimulus was perceived, and none did so when it was not perceived.

The pattern of activity was entirely different in the ITC. David L. Sheinberg, now at Brown University, and I recorded from this area after training monkeys to report their perceptions during rivalry between complex visual patterns, such as images of humans, animals and various man-made objects. We found that almost all neurons, about 90 percent, responded vigorously when their preferred pattern was perceived but that their activity was profoundly inhibited when this pattern was not being experienced.

So it seems that by the time visual signals reach the ITC, the great majority of neurons are responding in a way that is linked to perception. Frank Tong, Ken Nakayama and Nancy Kanwisher of Harvard University have used functional magnetic resonance imaging (fMRI)—which yields pictures of brain activity by measuring increases in blood flow in specific areas of the brain—to study people experiencing binocular rivalry. They found that the ITC was particularly active when the subjects reported that they were seeing images of faces.

In short, most of the neurons in the earlier stages of the visual pathway responded mainly to whether their preferred visual stimulus was in view or not, although a few showed behavior that could be related to changes in the animal's perception. In the later stages of processing, on the other hand, the proportion whose activity reflected the animal's perception increased until it reached 90 percent.



IMAGES OF BRAIN ACTIVITY are from an anesthetized monkey that was presented with a rotating, high-contrast visual stimulus (*lower left*). These views, taken using functional magnetic resonance imaging, show that even though the monkey is unconscious, its vision-processing areas—including the lateral geniculate nuclei (LGN), primary visual cortex (V1) and medial temporal cortex (MT/V5)—are busy.

A critic might object that the changing perceptions that monkeys report during binocular rivalry could be caused by the brain suppressing visual information at the start of the visual pathway, first from one eye and then from the other, so that the brain perceives a single image at any given time. If that were happening, changing neural activity and perceptions would simply represent the result of input that had switched from one eye to the other and would not be relevant to visual consciousness in other situations. But experimental evidence shows decisively that input from both eyes is continuously processed in the visual system during binocular rivalry.

We know this because it turns out that in humans, binocular rivalry produces its normal slow alternation of perceptions even if the competing stimuli are switched rapidly—several times per second—between the two eyes. If rivalry were merely a question of which eye the brain is paying attention to, the rivalry phenomenon would vanish when stimuli are switched quickly in this way. (The viewer would see, rather, a rapid alternation of the stimuli.) The observed persistence of slowly changing rivalrous perceptions when stimuli are switched strongly suggests that rivalry occurs because alternate stimulus representations compete in the visual pathway. Binocular rivalry thus affords an opportunity to study how the visual system decides what we see even when both eyes see (almost) the same thing.

A Perceptual Puzzle

WHAT DO THESE FINDINGS reveal about visual awareness? First, they show that we are unaware of a great deal of activity in our brains. We have long known

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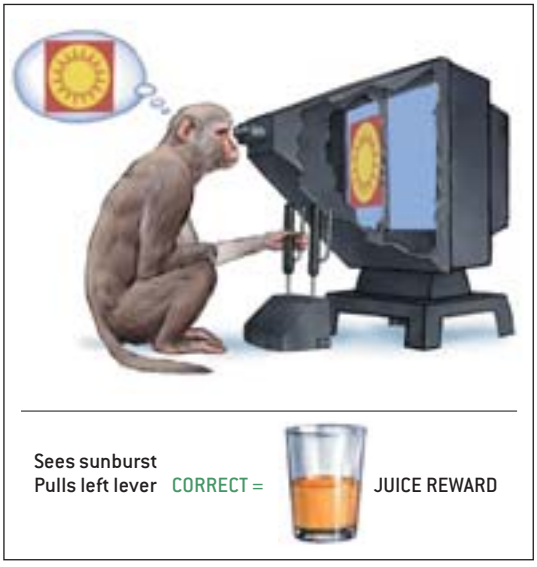
KEEPING MONKEYS (AND EXPERIMENTERS) HONEST

One possible objection to the experiments described in the main article is that the monkeys might have been inclined to cheat to earn their juice rewards. We are, after all, unable to know directly what a monkey (or a human) thinks or perceives at a given time. Because our monkeys were interested mainly in drinking juice rather than in understanding how consciousness arises from neuronal activity, it is possible that they could have developed a response strategy that appeared to reflect their true perceptions but really did not.

In the training session depicted below, for example, the monkey was being taught to pull the left lever only when it saw a sunburst and the right lever only when it saw a cowboy. We were able to ensure that the monkey continued to report truthfully by



that we are mostly unaware of the activity in the brain that maintains the body in a stable state—one of its evolutionarily most ancient tasks. Our experiments show that we are also unaware of much of the neural activity that generates—at least in part—our conscious experiences.

We can say this because many neurons in our brains respond to stimuli that we are not conscious of. Only a tiny fraction of neurons seem to be plausible candidates for what physiologists call the "neural correlate" of conscious perception—that is, they respond in a manner that reliably reflects perception.

We can say more. The small number of neurons whose behavior reflects perception are distributed over the entire visual pathway, rather than being part of a single area in the brain. Even though the ITC clearly has many more neurons that behave this way than those in other regions do, such neurons may be found elsewhere in future experiments. Moreover, other brain regions may be responsible for any decision resulting from whatever stimulus reaches consciousness. Erik D. Lumer and his colleagues at University College London have studied that possibility using fMRI. They showed that in humans the temporal lobe is activated during the conscious experience of a stimulus, as we found in monkeys. But other regions, such as the parietal and the prefrontal cortical areas, are activated precisely at the time at which a subject reports that the stimulus changes.

Further data about the locations of and connections between neurons that correlate with conscious experience will tell us more about how the brain generates awareness. But the findings to date already strongly suggest that visual awareness cannot be thought of as the end product of such a hierarchical series of processing stages. Instead it involves the entire visual pathway as well as the frontal parietal areas, which are involved in higher cognitive processing. The activity of a significant minority of neurons reflects what is consciously seen even in the lowest levels we looked at, V1 and V2; it is only the proportion of active neurons that increases at higher levels in the pathway.

It is not clear whether the activity of neurons in the very early areas is determined by their connections with other neurons in those areas or is the result of top-down, "feedback" connections emanating from the temporal or parietal lobes. Visual information flows from higher levels down to the lower ones as well as in the opposite direction. Theoretical studies indicate that systems with this kind of feedback can exhibit complicated patterns of behavior, including multiple stable states. Different stable states maintained by top-down feedback may correspond to different states of visual consciousness.

One important question is whether the activity of any of the neurons we have identified truly determine an animal's conscious perception. It is, after all, conceivable that these neurons are merely

MATT COLLINS

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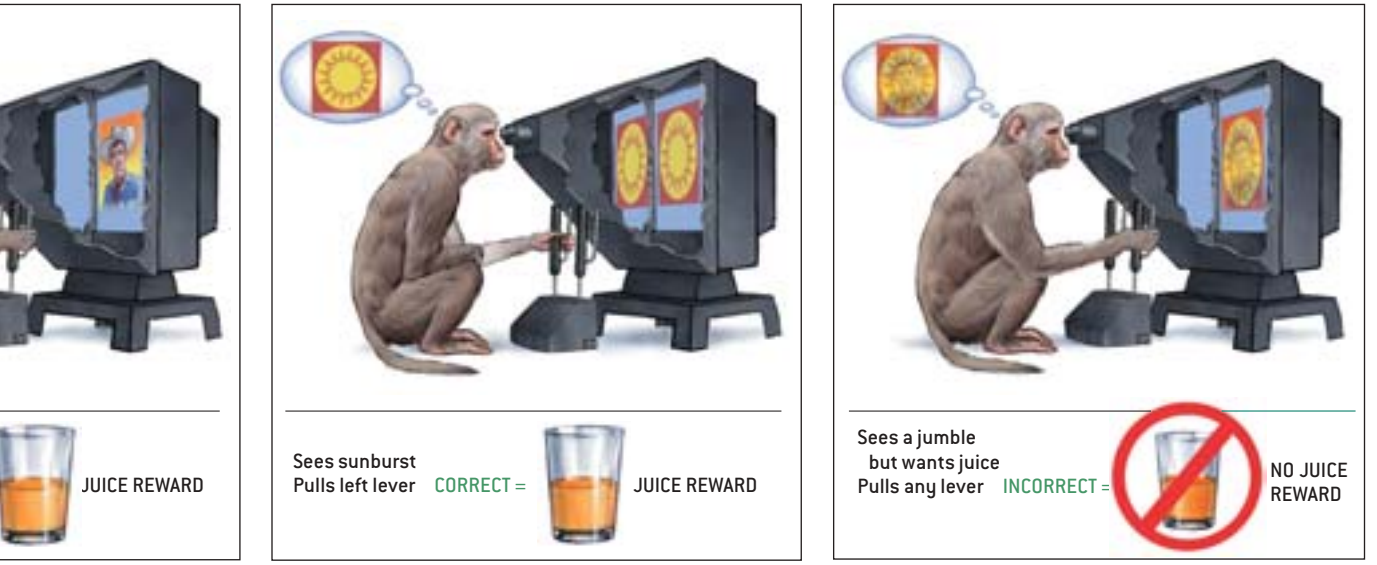
interjecting instances in which no rivalrous stimuli were shown (*below*). During these occasions, there was a "right" answer to what was perceived, and if the monkey did not respond correctly, the trial—and thus the opportunity to earn more juice rewards—was immediately ended. Similarly, if the monkey pulled any lever when presented with a jumbled image, in which the sunburst and the cowboy were superimposed (*last panel*), we knew the monkey was lying in an attempt to get more juice.

Our results indicate that monkeys report their experiences accurately. Even more convincing is our observation that monkeys and humans tested with the same apparatus perform at similar levels in different tasks. —*N.K.L.*



under the control of some other unknown part of the brain that actually determines conscious experience.

Elegant experiments conducted by William T. Newsome and his colleagues at Stanford University suggest that in area MT/V5, at least, neuronal activity can indeed determine directly what a monkey perceives. Newsome first identified neurons that selectively respond to a stimulus moving in a particular direction, then artificially activated them with small electric currents. The monkeys reported perceiving motion corresponding to the artificial activation even when stimuli were not moving in the direction indicated.

It will be interesting to see whether neurons of different types, in the ITC and possibly in lower levels, are also directly implicated in mediating consciousness. If they are, we would expect that stimulating or temporarily inactivating them would change an animal's reported perception during binocular rivalry.

A fuller account of visual awareness will also have to consider results from experiments on other cognitive processes, such as attention or what is termed working memory. Experiments by Robert Desimone and his colleagues at the National Institute of Mental Health reveal a remarkable resemblance between the competitive interactions observed during binocular rivalry and processes implicated in attention. Desimone and his colleagues train monkeys to report when they see stimuli for which they have been given cues in advance. Here, too, many neurons respond in a way that depends on what stimulus the animal expects to see or where it expects to see it. It is of obvious interest to know whether those neurons are the same ones as those firing only when a pattern reaches awareness during binocular rivalry.

The picture of the brain that starts to emerge from these studies is of a system whose processes create states of consciousness in response not only to sensory inputs but also to internal signals representing expectations based on past experiences. In principle, scientists should be able to trace the networks that support these interactions. The task is huge, but our success in identifying neurons that reflect consciousness is a good start. SA

MORE TO EXPLORE

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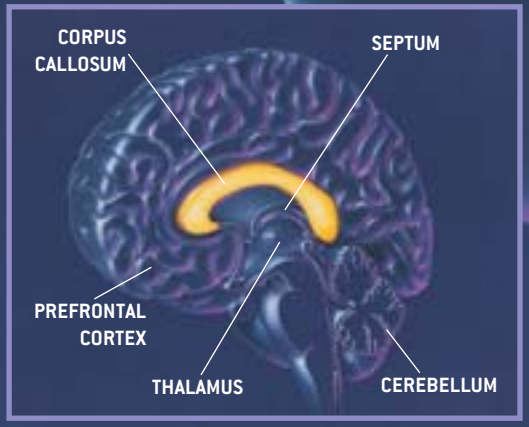

JOHN W. KARAPELOU

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Groundbreaking work over four decades has led to ongoing insights about brain organization and consciousness

The Split Brain Revisited

By Michael S. Gazzaniga

About 35 years ago in *Scientific American,* I wrote about dramatic new studies of the brain.

Three patients who were seeking relief from epilepsy had undergone surgery that severed the corpus callosum—the superhighway of neurons connecting the halves of the brain. By working with these patients, my colleagues Roger W. Sperry, Joseph E. Bogen, P. J. Vogel and I witnessed what happened when the left and the right hemispheres were unable to communicate with each other.

It became clear that visual information no longer moved between the two sides. If we projected an image to the right visual field—that is, to the left hemisphere, which is where information from the right field is processed—the patients could describe what they saw. But when the same image was displayed to the left visual field, the patients drew a blank: they said they didn't see anything. Yet if we asked them to point to an object similar to the one being projected, they could do so with ease. The right brain saw the image and could mobilize a nonverbal response. It simply couldn't talk about what it saw.

The same proved true for touch, smell and sound. Additionally, each half of the brain could control the upper muscles of both arms, but the muscles manipulating hand movement could be orchestrated only by the contralateral hemisphere. In other words, the right hemisphere could control only the left hand and the left hemisphere, only the right hand.

Ultimately, we discovered that the two hemispheres control vastly different aspects of thought and action. Each half has its own specialization and thus its own limitations and advantages. The left brain is dominant for language and speech. The right excels at visual-motor tasks.

In the intervening decades, split-brain research has continued to illuminate many areas of neuroscience. Not only have we and others learned even more about how the hemispheres differ, but we also have been able to understand how they communicate once they have been separated. Split-brain studies have shed light on language, on mechanisms of perception and attention, and on brain organization as well as the potential seat of false memories. Perhaps most intriguing has been the contribution of these studies to our understanding of consciousness and evolution.

The original split-brain studies raised many interesting questions, including whether the distinct halves could still "talk" to each other and what role this communication played in thought and action. There are several bridges of neurons, called commissures, that connect the hemispheres. The corpus callosum is the largest and typically the one severed during surgery for epilepsy. But what of the many other, smaller commissures?

BRAIN WIRING is, in many cases, contralateral (*left*). The right hemisphere processes information from the left visual field, whereas the left hemisphere processes data from the right visual field. For hand movement, the right hemisphere controls the left hand; the left hemisphere controls the right. Both hemispheres dictate upper-arm movement. The two hemispheres are connected by neuronal bridges called commissures. The largest of these, and the one severed during split-brain operations, is the corpus callosum.

Remaining Bridges

BY STUDYING THE ATTENTIONAL SYSTEM, researchers have been able to address this question. Attention involves many structures in the cortex and the subcortex—the older, more primitive part of our brains. In the 1980s Jeffrey D. Holtzman of Cornell University Medical College found that each hemisphere is able to direct spatial attention not only to its own sensory sphere but also to certain points in the sensory sphere of the opposite, disconnected hemisphere. This discovery suggests that the attentional system is common to both hemispheres—at least with regard to spatial information—and can still operate via some remaining interhemispheric connections.

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Holtzman's work was especially intriguing because it raised the possibility that there were finite attentional "resources." He posited that working on one kind of task uses certain brain resources; the harder the task, the more of these resources are needed—and the more one half of the brain must call on the subcortex or the other hemisphere for help. In 1982 Holtzman led the way again, discovering that, indeed, the harder one half of a split brain worked, the harder it was for the other half to carry out another task simultaneously.

Investigations by Steve J. Luck of the University of Iowa, Steven A. Hillyard and his colleagues at the University of California at San Diego and G. Ronald Mangun, now at the Duke University School of Medicine, have shown that another aspect of attention is also preserved in the split brain. They looked at what happens when a person searches a visual field for a pattern or an object. The researchers found that split-brain patients perform better than normal people do in some of these visual-searching tasks. The intact brain appears to inhibit the search mechanisms that each hemisphere naturally possesses.

The left hemisphere, in particular, can exert powerful control over such tasks. Alan Kingstone of the University of British Columbia found that the left hemisphere is "smart" about its search strategies, whereas the right is not. In tests in which a person can deduce how to search efficiently an array of similar items for an odd exception, the left does better than the right. Thus, it seems that the more competent left hemisphere can hijack the intact attentional system.

Although these and other studies indicated that some communication between the split hemispheres remains, other apparent interhemispheric links proved illusory. I conducted an experiment with Kingstone that nearly misled us on this front. We flashed two words to a patient and then asked him to draw what he saw. "Bow" was flashed to one hemisphere and "arrow" to the other. To our surprise, our patient drew a bow and arrow! It appeared that he had internally integrated the information in one hemisphere, which then directed the drawn response [*see illustration on page 30*].

We were wrong. We learned that integration had taken place on the paper, not in the brain. One hemisphere had drawn its item—the bow—and then the other had gained control of the writing hand, drawing its stimulus—the arrow—on top of the bow. We discovered this chimera by giving less easily integrated word pairs like "sky" and "scraper." The subject did not draw a tall building; instead he drew the sky over a picture of a scraper.

The Limits of Extrapolation

IN ADDITION TO HELPING neuroscientists determine which systems still work and which are severed along with the corpus callosum, studies of communication between the hemispheres led to an important finding about the limits of nonhuman studies. For many years, neuroscientists have examined the brains of monkeys and other creatures to explore the ways in which the human brain operates. Indeed, it has been a common belief that the brains of our closest relatives have an organization and function largely similar, if not identical, to our own.

Split-brain research has shown that this assumption can be spurious. Although some structures and functions are remarkably alike, differences abound. The anterior commissure provides one dramatic example. This small structure lies somewhat below the corpus callosum. When this commissure is left intact in otherwise split-brain monkeys, the animals retain the ability to transfer visual information from one hemisphere to the other. People, however, do not transfer visual information in any way. Hence, the same structure carries out different functions in different species.

Even extrapolating between people can be dangerous. One of our first striking findings was that the left brain could freely process language and speak about its experience. Although the right was not so free, we found that it could process some language. Among other skills, the right hemisphere could match words to pictures, do spelling and rhyming, and categorize objects. Although we never found any sophisticated capacity for syntax in that half of the brain, we believed the extent of its lexical knowledge to be quite impressive.

Our first three cases proved to be unusual. Most people's right hemispheres cannot handle even the most rudimentary language, contrary to what we initially observed. This finding is in keeping with other neurological data, particularly those from stroke victims. Damage to the left hemisphere is far more detrimental to language function than is damage to the right.

Nevertheless, there exists a great deal of plasticity and individual variation. One patient, dubbed J.W., developed the capacity to speak out of the right hemisphere—13 years after surgery. J.W. can now occasionally speak about information presented to the left or to the right brain.

Kathleen B. Baynes of the University of California at Davis reports another unique case. A left-handed patient spoke out of her left brain after split-brain surgery—not a surprising finding in itself. But the patient could *write* only out of her right,

We and others have learned more about how the hemispheres differ and HOW THEY COMMUNICATE.

THE AUTHOR

MICHAEL S. GAZZANIGA is professor of cognitive neuroscience and director of the Center for Cognitive Neuroscience at Dartmouth College. He received his Ph.D. at the California Institute of Technology, where he, Roger W. Sperry and Joseph E. Bogen initiated split-brain studies. Since then, he has published in many areas and is credited with launching the field of cognitive neuroscience in the early 1980s. Gazzaniga likes to ski and to arrange small, intense intellectual meetings in exotic places.

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nonspeaking hemisphere. This dissociation confirms the idea that the capacity to write need not be associated with the capacity for phonological representation. Put differently, writing appears to be an independent system, an invention of the human species. It can stand alone and does not need to be part of our inherited spoken language system.

Brain Modules

DESPITE MYRIAD EXCEPTIONS, the bulk of split-brain research has revealed an enormous degree of lateralization, or specialization in each hemisphere. As investigators have struggled to understand how the brain achieves its goals and how it is organized, the lateralization revealed by split-brain studies has figured into what is called the modular model. Research in cognitive science, artificial intelligence, evolutionary psychology and neuroscience has directed attention to the idea that brain and mind are built from discrete units, or modules. These modules carry out specific functions, working in concert to assist the mind's information-processing demands.

Within that modular system, the left hemisphere has proved quite dominant for major cognitive activities, such as problem solving. Split-brain surgery does not seem to affect these functions. It is as if the left hemisphere has no need for the vast computational power of the other half of the brain to carry out high-level activities. The right hemisphere, meanwhile, is severely deficient in difficult problem solving.

Joseph E. LeDoux of New York University and I discovered this quality of the left brain almost 25 years ago. We had asked a simple question: How does the left hemisphere respond to behaviors produced by the silent right brain? Each hemisphere was presented a picture that related to one of four pictures placed in front of the split-brain subject. The left and the right hemispheres easily picked the correct card. The left hand pointed to the right hemisphere's choice and the right hand to the left hemisphere's choice [*see illustration at right*].

We then asked the left hemisphere, the only one that can talk, why the left hand was pointing to the object. It did not know, because the decision to point was made in the right hemisphere. Yet it quickly made up an explanation. We dubbed this creative, narrative talent the interpreter mechanism.

This fascinating ability has been studied to determine how the left hemisphere interpreter affects memory. Elizabeth A. Phelps, now at New York University, Janet Metcalfe of Columbia University and Margaret Funnell of Dartmouth College found that the two hemispheres differ in their ability to process new data. When presented with new information, people usually remember much of what they experience. When questioned, they also usually claim to remember things that were not truly part of the experience. If split-brain patients are given such tests, the left hemisphere generates many false reports. But the right brain does not; it provides a much more veridical account.

This finding may help researchers determine where and how false memories develop. There are several views about when in the cycle of information processing such memories are laid down. Some researchers suggest they develop early in the cycle, that erroneous accounts are actually encoded at the time of the event. Others believe false memories reflect an error in reconstructing past experience: in other words, that people develop a schema about what happened and retrospectively fit untrue events—that are nonetheless consistent with the schema—into their recollection of the original experience.

The left hemisphere exhibits certain characteristics that support the latter view. First, developing such schemata is exactly what the left hemisphere interpreter excels at. Second, Funnell discovered that the left hemisphere has an ability to determine the source of a memory, based on the context or the surrounding events. Her work indicates that the left hemisphere actively

The Interpreter

OUR PERSONAL NARRATIVES originate in the left hemisphere. My colleagues and I studied this phenomenon by administering a test. Each hemisphere was shown four small pictures, one of which related to a larger picture also presented to that hemisphere. The patient had to choose the most appropriate small picture.

As seen below, the right hemisphere—that is, the left hand—correctly picked the shovel for the snowstorm; the right hand, controlled by the left hemisphere, correctly picked the chicken to go with the bird's foot. Then we asked the patient why the left hand—or right hemisphere—was pointing to the shovel. Because only the left hemisphere retains the ability to talk, it answered. But because it could not know why the right hemisphere was doing what it was doing, it made up a story about what it could see—namely, the chicken. It said the right hemisphere chose the shovel to clean out a chicken shed. —*M.S.G.*

JOHN W. KARAPELOU

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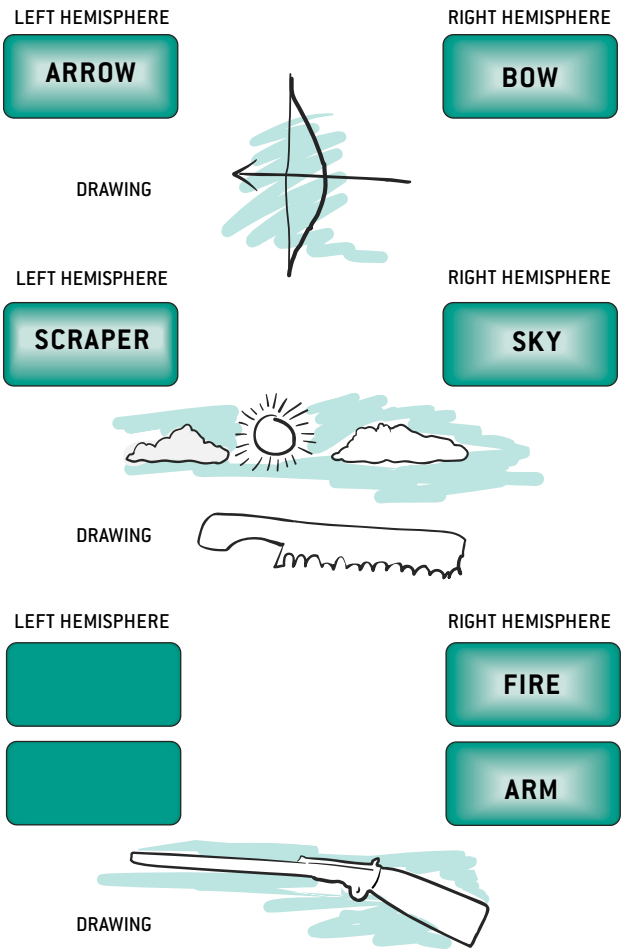
Testing for Synthesis

ABILITY TO SYNTHESIZE information between hemispheres is lost after split-brain surgery, as this experiment shows. One hemisphere of a patient was flashed a card with the word "bow"; the other hemisphere saw "arrow." Because the patient drew a bow and arrow, my colleagues and I assumed the two hemispheres were still able to communicate with each other—despite the severing of the corpus callosum—and had integrated the words into a meaningful composite.

The next test proved us wrong. We flashed "sky" to one hemisphere and "scraper" to the other. The resulting image revealed that the patient was not synthesizing information: sky atop a comblike scraper was drawn, rather than a tall building. One hemisphere drew what it had seen, then the other drew its word. In the case of bow and arrow, the superposition of the two images misled us because the picture appeared integrated. Finally, we tested to see whether each hemisphere could, on its own, integrate words. We flashed "fire" and then "arm" to the right hemisphere. The left hand drew a rifle rather than an arm on fire, so it was clear that each hemisphere was capable of synthesis. —*M.S.G.*



places its experiences in a larger context, whereas the right simply attends to the perceptual aspects of the stimulus.

These findings all suggest that the interpretive mechanism of the left hemisphere is always hard at work, seeking the meaning of events. It is constantly looking for order and reason, even when there is none—which leads it continually to make mistakes. It tends to overgeneralize, frequently constructing a potential past as opposed to a true one.

The Evolutionary Perspective

GEORGE L. WOLFORD of Dartmouth has lent even more support to this view of the left hemisphere. In a simple test that requires a person to guess whether a light is going to appear on the top or bottom of a computer screen, humans perform inventively. The experimenter manipulates the stimulus so that the light appears on the top 80 percent of the time but in a random sequence. While it quickly becomes evident that the top button is being illuminated more often, people invariably try to figure out the entire pattern or sequence—and they truly believe they can. Yet by adopting this strategy, they are correct only 68 percent of the time. If they always pressed the top button, they would be correct 80 percent of the time.

But rats and other animals are more likely to "learn to maximize," pressing only the top button. The right hemisphere acts in the same way: it does not try to interpret its experience and find deeper meaning. It continues to live only in the present—and to be correct 80 percent of the time. But the left, when asked to explain why it is attempting to figure the whole sequence, always comes up with a theory, no matter how outlandish.

This narrative phenomenon is best explained by evolutionary theory. The human brain, like any brain, is a collection of neurological adaptations established through natural selection. These adaptations each have their own representation—that is, they can be lateralized to specific regions or networks in the brain. But throughout the animal kingdom, capacities are generally not lateralized. Instead they tend to be found in both hemispheres to roughly equal degrees. And although monkeys show some signs of lateral specialization, these are rare and inconsistent.

For this reason, it has always appeared that the lateralization seen in the human brain was an evolutionary add-on—mechanisms or abilities that were laid down in one hemisphere only. We recently stumbled across an amazing hemispheric dissociation that challenges this view. It forced us to speculate that some lateralized phenomena may arise from a hemisphere's losing an ability, not gaining it.

In what must have been fierce competition for cortical space, the evolving primate brain would have been hard-pressed to gain new faculties without losing old ones. Lateralization could have been its salvation. Because the two hemispheres are connected, mutational tinkering with a homologous cortical region could give rise to a new function—yet not cost the animal, because the other side would remain unaffected.

Paul M. Corballis and Robert Fendrich of Dartmouth, Robert M. Shapley of New York University and I studied in many split-brain patients the perception of what are called illusory con-

LAURIE GRACE

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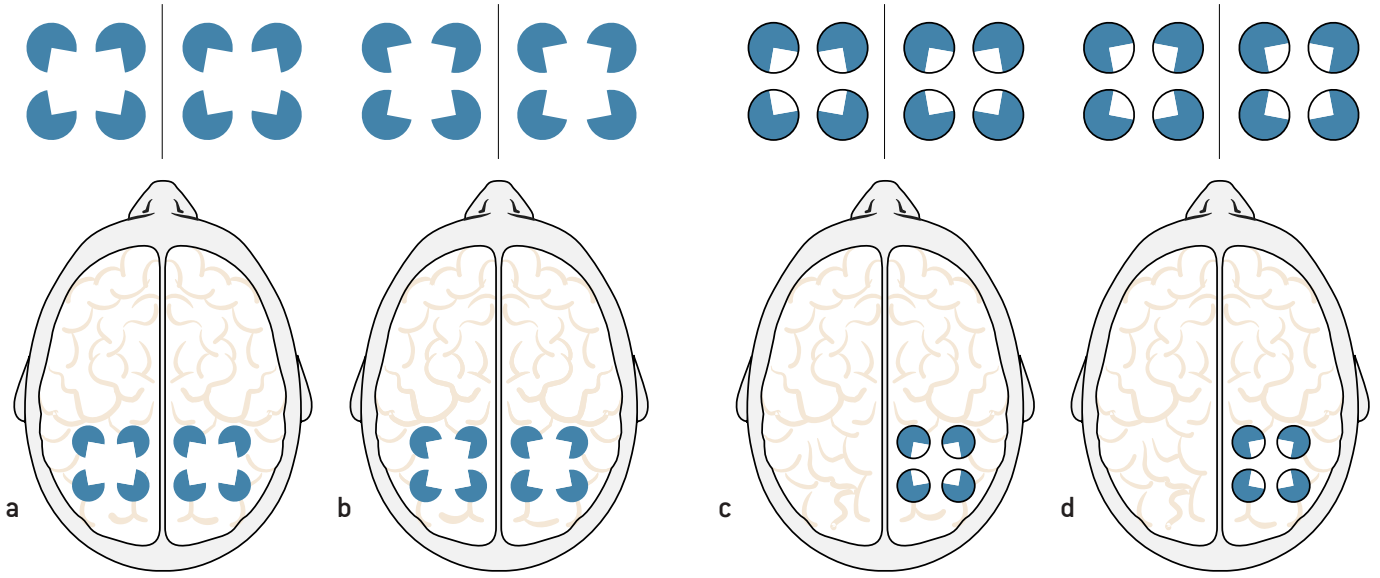
Looking for Illusions

ILLUSORY CONTOURS REVEAL that the human right brain can process some things that the left cannot. Both hemispheres can "see" whether the illusory rectangles of this experiment are fat (*a*) or thin (*b*). But when outlines are added, only the right brain can still tell the difference (*c* and *d*). In mice, however, both hemispheres can consistently perceive these differences. For a rodent to perform better than we do suggests that some capabilities were lost from one hemisphere or the other as the human brain evolved. New capabilities may have squeezed out old ones in a race for space. —*M.S.G.*



tours. Earlier work had suggested that seeing the well-known illusory contours of the late Gaetano Kanizsa of the University of Trieste was the right hemisphere's specialty. Our experiments revealed a different situation.

We discovered that both hemispheres could perceive illusory contours—but that the right hemisphere was able to grasp certain perceptual groupings that the left could not. Thus, whereas both hemispheres in a split-brain person can judge whether the illusory rectangles are fat or thin when no line is drawn around the openings of, say, "Pacman" figures, only the right can continue to make the judgment after a line has been drawn [*see illustration above*]. This setup is referred to as the amodal version of the test.

What is so interesting is that Kanizsa himself demonstrated that mice can do the amodal version. That a lowly mouse can perceive perceptual groupings, whereas a human's left hemisphere cannot, suggests that a capacity has been lost. Could it be that the emergence of a human capacity like language—or an interpretive mechanism—chased this perceptual skill out of the left brain? We think so, and this opinion gives rise to a fresh way of thinking about the origins of lateral specialization.

Our uniquely human skills may well be produced by minute and circumscribed neuronal networks. And yet our highly modularized brain generates the feeling in all of us that we are integrated and unified. How so, given that we are a collection of specialized modules?

The answer may be that the left hemisphere seeks explanations for why events occur. The advantage of such a system is obvious. By going beyond the simple observation of events and asking why they happened, a brain can cope with these same events better, should they happen again.

Realizing the strengths and weaknesses of each hemisphere prompted us to think about the basis of mind, about this overarching organization. After many years of fascinating research on the split brain, it appears that the inventive and interpreting left hemisphere has a conscious experience very different from that of the truthful, literal right brain. Although both hemispheres can be viewed as conscious, the left brain's consciousness far surpasses that of the right. Which raises another set of questions that should keep us busy for the next 30 years or so. SA

MORE TO EXPLORE

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sex differences in the brain

BY DOREEN KIMURA

MEN AND WOMEN DIFFER not only in their physical attributes and reproductive function but also in many other characteristics, including the way they solve intellectual problems. For the past few decades, it has been ideologically fashionable to insist that these behavioral differences are minimal and are the consequence of variations in experience during development before and after adolescence. Evidence accumulated more recently, however, suggests that the effects of sex hormones on brain organization occur so early in life that from the start the environment is acting on differently wired brains in boys and girls. Such effects make evaluating the role of experience, independent of physiological predisposition, a difficult if not dubious task. The biological bases of sex differences in brain and behavior have become much better known through increasing numbers of behavioral, neurological and endocrinological studies.

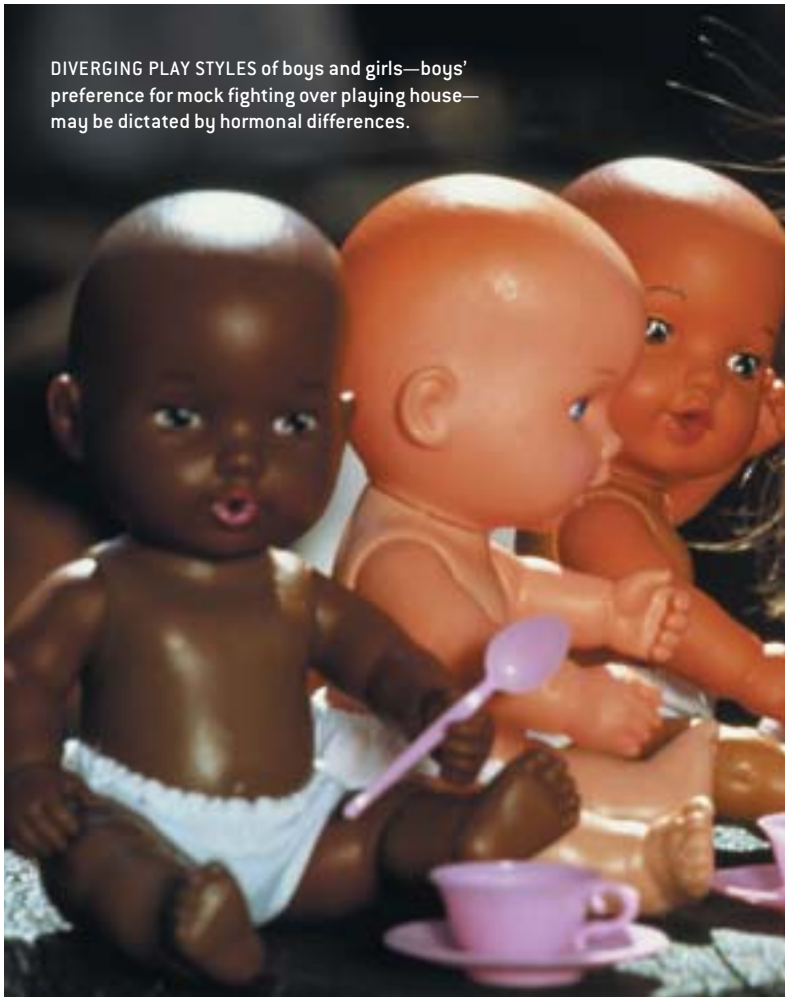
We know, for instance, from observations of both humans and nonhumans that males are more aggressive than females, that young males engage in more rough-and-tumble play than females and that females are more nurturing. We also know that in general males are better at a variety of spatial or navigational tasks. How do these and other sex differences come about? Much of our information and many of our ideas about how sexual differentiation takes place derive from research on animals. From such investigations, it appears that perhaps the most important factor in the differentiation of males and females and indeed in differentiating individuals within a sex is the level of exposure to various sex hormones early in life.

In most mammals, including humans, the developing organism has the potential to be male or female. Producing a male, however, is a complex process. When a Y chromosome is present, testes, or male gonads, form. This development is the critical first step toward becoming a male. When no Y chromosome is present, ovaries form.

Testes produce male hormones, or androgens (testosterone chief among them), which are responsible not only for transformation of the genitals into male organs but also for organization of corresponding male behaviors early in life. As with genital formation, the intrinsic tendency that occurs in the absence of masculinizing hormonal influence, according to seminal studies by Robert W. Goy of the University of Wisconsin, is to develop female genital structures and behavior. Female anatomy and probably most behavior associated with females are thus the default modes in the absence of androgens.

If a rodent with functional male genitals is deprived of androgens immediately after birth (either by castration or by the

MEN AND WOMEN DISPLAY PATTERNS OF BEHAVIORAL AND COGNITIVE DIFFERENCES THAT REFLECT VARYING HORMONAL INFLUENCES ON BRAIN DEVELOPMENT



DIVERGING PLAY STYLES of boys and girls—boys' preference for mock fighting over playing house—may be dictated by hormonal differences.

Updated from Men, *Summer 1999 (Scientific American Presents)*

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administration of a compound that blocks androgens), male sexual behavior, such as mounting, will be reduced, and more female sexual behavior, such as lordosis (arching of the back when receptive to coitus), will be expressed. Likewise, if androgens are administered to a female directly after birth, she will display more male sexual behavior and less female behavior in adulthood. These lifelong effects of early exposure to sex hormones are characterized as "organizational" because they appear to alter brain function permanently during a critical period in prenatal or early postnatal development. Administering the same sex hormones at later stages or in the adult has no similar effect.

Not all the behaviors that distinguish males are categorized at the same time, however. Organization by androgens of the male-typical behaviors of mounting and of rough-and-tumble play, for example, occur at different times prenatally in rhesus monkeys.

The area in the brain that regulates female and male reproductive behavior is the hypothalamus. This tiny structure at the base of the brain connects to the pituitary, the master endocrine gland. It has been shown that a region of the hypothalamus is visibly larger in male rats than in females and that this size difference is under hormonal control. Scientists have also found parallel sex differences in a clump of nerve cells in the human brain—parts of the interstitial nucleus of the anterior hypothalamus—that is larger in men than in women. Even sexual orientation and gender identity have been related to anatomical variation in the hypothalamus. Other researchers, Jiang-Ning Zhou of the Netherlands Institute of Brain Research and his colleagues there and at Free University in Amsterdam, observed another part of the hypothalamus to be smaller in male-to-female transsexuals than in a male control group. These findings are consistent with suggestions that sexual orientation and gender identity have a significant biological component.

SUE ANN MILLER *Stone (below)*; DIRK DOUGLAS *Corbis (right)*

Hormones and Intellect

WHAT OF DIFFERENCES in intellectual function between men and women? Major sex differences in function seem to lie in patterns of ability rather than in overall level of intelligence (measured as IQ), although some researchers, such as Richard Lynn of the University of Ulster in Northern Ireland, have argued that there exists a small IQ difference favoring human males. Differences in intellectual pattern refer to the fact that people have different intellectual strengths. For example, some people are especially good at using words, whereas others are better at dealing with external stimuli, such as identifying an object in a different orientation. Two individuals may have differing cognitive abilities within the same level of general intelligence.

Sex differences in problem solving have been systematically studied in adults in laboratory situations. On average, men perform better than women at certain spatial tasks. In particular, men seem to have an advantage in tests that require the subject to imagine rotating an object or manipulating it in some other way. They also outperform women in mathematical reasoning tests and in navigating their way through a route. Fur-

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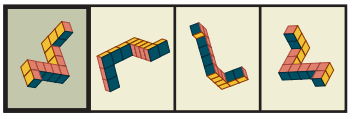
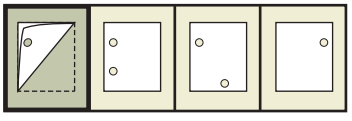
Problem-Solving Tasks Favoring Men

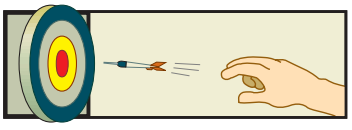
Men tend to perform better than women on certain spatial tasks. They do well on tests that involve mentally rotating an object or manipulating it in some fashion, such as imagining turning this three-dimensional object



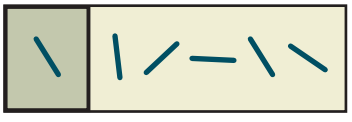
or determining where the holes punched in a folded piece of paper will fall when the paper is unfolded:



Men also are more accurate than women at target-directed motor skills, such as guiding or intercepting projectiles:



They do better at matching lines with identical slopes:



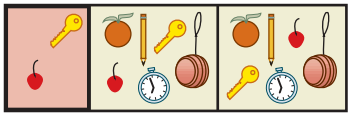
And men tend to do better than women on tests of mathematical reasoning:

1,100	If only 60 percent of seedlings will survive, how many must be planted to obtain 660 trees?

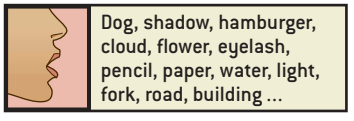
Problem-Solving Tasks Favoring Women

Women tend to perform better than men on tests of perceptual speed in which subjects must rapidly identify matching items—for example, pairing the house on the far left with its twin:

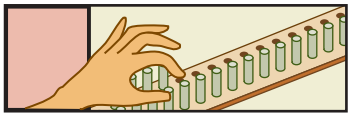
In addition, women remember whether an object, or a series of objects, has been displaced:



When they are read a story, paragraph or a list of unrelated words, women demonstrate better recall:



Women do better on precision manual tasks—that is, those involving fine-motor coordination—such as placing the pegs in holes on a board:



And women do better than men on mathematical calculation tests:

77	$14 \times 3 - 17 + 52$
43	$2\,(15 + 3) + 12 - \frac{15}{3}$

ther, men exhibit more accuracy in tests of target-directed motor skills—that is, in guiding or intercepting projectiles.

Women, on average, excel on tests that measure recall of words and on tests that challenge the person to find words that begin with a specific letter or fulfill some other constraint. They also tend to be better than men at rapidly identifying matching items and performing certain precision manual tasks, such as placing pegs in designated holes on a board.

In examining the nature of sex differences in navigating routes, one study found that men completed a computer simulation of a maze or labyrinth task more quickly and with fewer errors than women did. Another study by different researchers used a path on a tabletop map to measure route learning. Their results showed that although men learned the route in fewer trials and with fewer errors, women remembered more of the landmarks, such as pictures of different types of buildings, than men did. These results and others suggest that women tend to use landmarks as a strategy to orient themselves in everyday life more than men do.

Other findings seemed also to point to female superiority in landmark memory. Researchers tested the ability of individuals to recall objects and their locations within a confined space—such as in a room or on a tabletop. In these studies, women were better able to remember whether items had changed places or not. Other investigators found that women were superior at a memory task in which they had to remember the locations of pictures on cards that were turned over in pairs. At this kind of object location, in contrast to other spatial tasks, women appear to have the advantage.

It is important to keep in mind that some of the average sex differences in cognition vary from slight to quite large and that men and women overlap enormously on many cognitive tests that show average differences. For example, whereas women perform better than men in both verbal memory (recalling words from lists or paragraphs) and verbal fluency (finding words that begin with a specific letter), we find a large difference in memory ability but only a small disparity for the fluency tasks. On the whole, variation between men and women tends to be smaller than deviations within each sex, but very large differences between the groups do exist—in men's high level of visual-spatial targeting ability, for one.

Although it used to be thought that sex differences in problem solving did not appear until puberty, the accumulated

DOREEN KIMURA AND JOHN MENGEL

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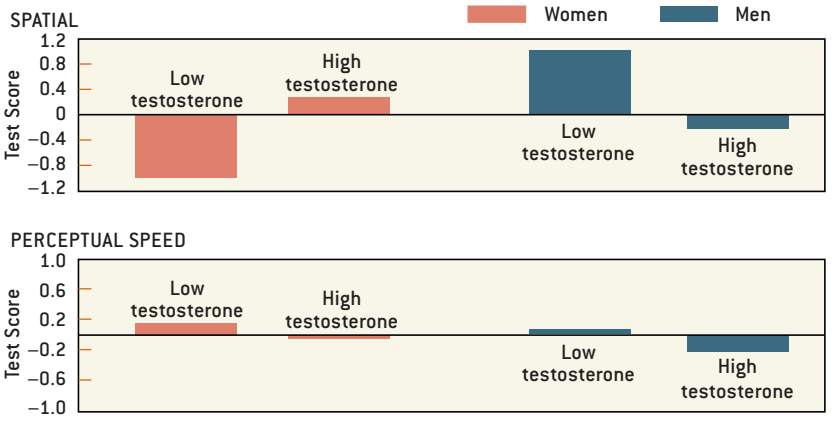

TESTOSTERONE LEVELS can affect performance on some tests [*see boxes on opposite page for examples of tests*]. Women with high levels of testosterone perform better on spatial tasks (*top*) than women with low levels do, but men with low levels outperform men with high levels. On a test of perceptual speed in which women usually excel (*bottom*), no relation was found between testosterone and performance.

evidence now suggests that some cognitive and skill differences are present much earlier. For example, researchers have found that three- and four-year-old boys were better at targeting and at mentally rotating figures within a clock face than girls of the same age were. Prepubescent girls, however, excelled at recalling lists of words.

Male and female rodents have also been found to solve problems differently. Christina L. Williams of Duke University has shown that female rats have a greater tendency to use landmarks in spatial learning tasks, as it appears women do. In Williams's experiment, female rats used landmark cues, such as pictures on the wall, in preference to geometric cues: angles and the shape of the room, for instance. If no landmarks were available, however, females used the geometric cues. In contrast, males did not use landmarks at all, preferring geometric cues almost exclusively.

Hormones and Behavior

WILLIAMS ALSO FOUND that hormonal manipulation during the critical period could alter these behaviors. Depriving newborn males of sex hormones by castrating them or administering hormones to newborn females resulted in a complete reversal of sex-typed behaviors in the adult animals. Treated males behaved like females and treated females, like males.

Structural differences may parallel behavioral ones. Lucia F. Jacobs, while at the University of Pittsburgh, discovered that the hippocampus—a region thought to be involved in spatial learning—is larger in several male species of rodents than in females. At present, there are insufficient data on possible sex differences in hippocampal size in human subjects.

One of the most compelling areas of evidence for hormonally influenced sex differences in humans comes from studies of girls exposed to excess androgens in the prenatal or neonatal stage. The production of abnormally large quantities of adrenal androgens can occur because of a genetic defect in a condition called congenital adrenal hyperplasia (CAH). Before the 1970s a similar condition also unexpectedly appeared in the offspring of pregnant women who took various synthetic steroids. Although the consequent masculinization of the genitals can be corrected by surgery and drug therapy can stop the overproduction of androgens, the effects of prenatal exposure on the brain are not reversed.

Sheri A. Berenbaum, while at Southern Illinois University at Carbondale, and Melissa Hines, then at the University of California at Los Angeles, observed the play behavior of CAH girls and compared it with that of their male and female siblings. Given a choice of transportation and construction toys, dolls and kitchen supplies, or books and board games, the CAH girls preferred the more typically masculine toys—for example, they played with cars for the same amount of time that boys did. Both the CAH girls and the boys differed from unaffected girls in their patterns of choice. Berenbaum also found that CAH girls had greater interest in male-typical activities and careers. Because there is every reason to think parents would be at least as likely to encourage feminine preferences in their CAH daughters as in their unaffected daughters, these findings suggest that these preferences were altered by the early hormonal environment.

Other researchers also found that spatial abilities that are typically better in males are enhanced in CAH girls. But in CAH boys the reverse was reported.

Such studies suggest that although levels of androgen relate to spatial ability, it is not simply the case that the higher the levels, the better the spatial scores. Rather studies point to some optimal level of androgen (in the low male range) for maximal spatial ability. This finding may also hold for men and math reasoning; in one study, low-androgen men tested higher.

The Biology of Math

SUCH FINDINGS are relevant to the suggestion by Camilla P. Benbow, now at Vanderbilt University, that high mathematical ability has a significant biological determinant. Benbow and her colleagues have reported consistent sex differences in mathematical reasoning ability that favor males. In mathematically talented youth, the differences were especially sharp at the upper end of the distribution, where males vastly outnumbered females. The same has been found for the Putnam competition, a very demanding mathematics examination. Benbow argues that these differences are not readily explained by socialization.

It is important to keep in mind that the relation between natural hormone levels and problem solving is based on correlational data. Although some form of connection between the two measures exists, we do not necessarily know how the association is determined, nor do we know what its causal basis is. We also know lit-

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tle at present about the relation between adult levels of hormones and those in early life, when abilities appear to become organized in the nervous system.

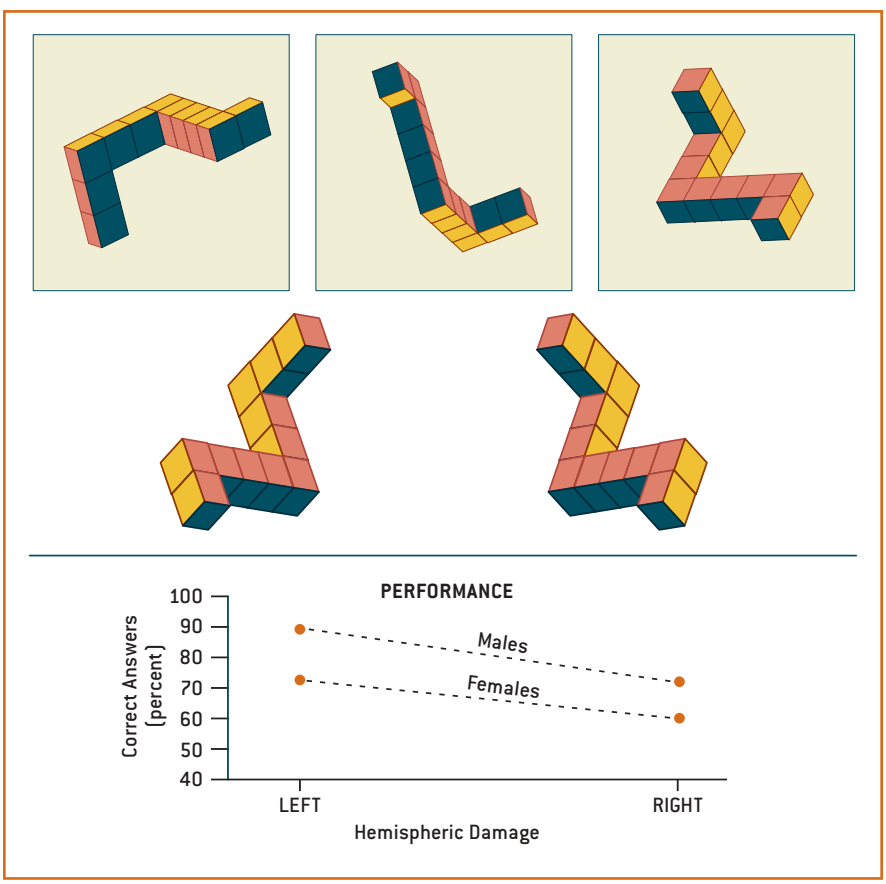
One of the most intriguing findings in adults is that cognitive patterns may remain sensitive to hormonal fluctuations throughout life. Elizabeth Hampson of the University of Western Ontario showed that women's performances at certain tasks changed throughout the menstrual cycle as levels of estrogen varied. High levels of the hormone were associated not only with relatively depressed spatial ability but also with enhanced speech and manual skill tasks. In addition, I have observed seasonal fluctuations in spatial ability in men: their performance is better in the spring, when testosterone levels are lower. Whether these hormonally linked fluctuations in intellectual ability represent useful evolutionary adaptations or merely the highs and lows of an average test level remains to be seen through further research.

A long history of studying people with damage to one half of their brain indicates that in most people the left hemisphere of the brain is critical for speech and the right for certain perceptual and spatial functions. Researchers studying sex differences have widely assumed that the right and left hemispheres of the brain are more asymmetrically organized for speech and spatial functions in men than in women.

This belief rests on several lines of research. Parts of the corpus callosum, a major neural system connecting the two hemispheres, as well as another connector, the anterior commissure, appear to be larger in women, which may permit better communication between hemispheres. Perceptual techniques that measure brain asymmetry in normal-functioning people sometimes show smaller asymmetries in women than in men, and damage to one brain hemisphere sometimes has less of an effect in women than the comparable injury in men does. My own data on patients with damage to one hemisphere of the brain suggest that for functions such as basic speech and spatial ability, there are no major sex differences in hemispheric asymmetry, although there may be such disparities in certain more abstract abilities, such as defining words.

If the known overall differences between men and women in spatial ability were related to differing dependence on the right brain hemisphere for such functions, then damage to that hemisphere might be expected to have a more devastating effect on spatial performance in men. My laboratory has studied the ability of patients with damage to one hemisphere of the brain to visualize the rotation of certain objects. As expected, for both sexes, those with damage to the right hemisphere got lower scores on these tests than those with damage to the left hemisphere did. Also, as anticipated, women did not do as well as men on this test. Damage to the right hemisphere, however, had no greater effect on men than on women.

The results of this study and others suggest that the normal differences between men and women on rotational and line orientation tasks need not be the result of different degrees of dependence on the right hemisphere. Some other brain systems may be mediating the higher performance by men.



RIGHT HEMISPHERE DAMAGE affects spatial ability to the same degree in both sexes (*graph*), suggesting that women and men rely equally on that hemisphere for certain spatial tasks. In one test of spatial-rotation performance, photographs of a three-dimensional object must be matched to one of two mirror images of the same object.

Patterns of Function

ANOTHER BRAIN difference between the sexes has been shown for speech and certain manual functions. Women incur aphasia (impairment of the power to produce and understand speech) more often after anterior damage than after posterior damage to the brain. In men, posterior damage more often affects speech. A similar pattern is seen in apraxia, difficulty in selecting appropriate hand movements, such as showing how to manipulate a particular object or copying the movements of the experimenter. Women seldom experience apraxia after left posterior damage, whereas men often do.

Men also incur aphasia from left hemisphere damage more often than women

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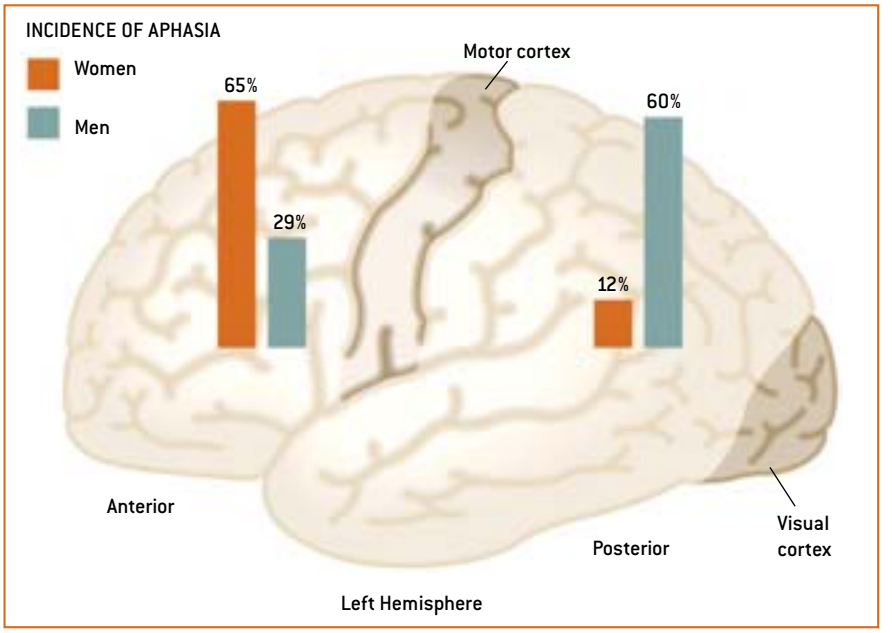
do. One explanation suggests that restricted damage within a hemisphere after a stroke more often affects the posterior region of the left hemisphere. Because men rely more on this region for speech than women do, they are more likely to be affected. We do not yet understand the effects on cognitive patterns of such divergent representation of speech and manual functions.

Although my laboratory has not found evidence of sex differences in functional brain asymmetry with regard to basic speech, movement or spatial-rotation abilities, we have found slight differences in some verbal skills. Scores on a vocabulary test and on a verbal fluency test, for instance, were slightly affected by damage to either hemisphere in women, but such scores were affected only by left hemisphere damage in men. These findings suggest that when using some more abstract verbal skills, women do use their hemispheres more equally than men do. But we have not found this to be true for all word-related tasks; for example, verbal memory appears to depend just as much on the left hemisphere in women as in men.

In recent years, new techniques for assessing the brain's activity—including functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), when used during various problem-solving activities—have shown promise for providing more information about how brain function may vary among normal, healthy individuals. The research using these two techniques has so far yielded interesting, yet at times seemingly conflicting, results.

Some research has shown greater differences in activity between the hemispheres of men than of women during certain language tasks, such as judging if two words rhyme and creating past tenses of verbs. Other research has failed to find sex differences in functional asymmetry. The different results may be attributed in part to different language tasks being used in the various studies, perhaps showing that the sexes may differ in brain organization for some language tasks but not for others.

The varying results may also reflect the complexity of these techniques. The brain is always active to some degree. So for any activity, such as reading aloud, the comparison activity—say, reading silently—is intended to be very similar. We then "subtract" the brain pattern that occurs during silent reading to find the brain pattern present while reading aloud. Yet such methods require dubious assumptions about what the subject is doing during either activity. In addition, the more complex the activity, the more difficult it is to know what is actually being measured after subtracting the comparison activity.



APHASIAS, or speech disorders, occur most often in women when damage is sustained in the anterior of the brain. In men, they occur more frequently when damage is in the posterior region. The data presented above derive from one set of patients.

Looking Back

TO UNDERSTAND human behavior—how men and women differ from one another, for instance—we must look beyond the demands of modern life. Our brains are essentially like those of our ancestors of 50,000 and more years ago, and we can gain some insight into sex differences by studying the differing roles men and women have played in evolutionary history. Men were responsible for hunting and scavenging, defending the group against predators and enemies, and shaping and using weapons. Women gathered food near the home base, tended the home, prepared food and clothing, and cared for small children. Such specialization would put different selection pressures on men and women.

Any behavioral differences between individuals or groups must somehow be mediated by the brain. Sex differences have been reported in brain structure and organization, and studies have been done on the role of sex hormones in influencing human behavior. But questions remain regarding how hormones act on human brain systems to produce the sex differences we described, such as in play behavior or in cognitive patterns.

The information we have from laboratory animals helps to guide our explanations, but ultimately these hypotheses must be tested on people. Refinements in brain-imaging techniques, when used in conjunction with our knowledge of hormonal influences and with continuing studies on the behavioral deficits after damage to various brain regions, should provide insight into some of these questions. SA

MORE TO EXPLORE

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new nerve cells for the adult brain

CONTRARY TO DOGMA, THE HUMAN BRAIN DOES PRODUCE NEW NERVE CELLS IN ADULTHOOD. CAN THIS LEAD TO BETTER TREATMENTS FOR NEUROLOGICAL DISEASES?

BY GERD KEMPERMANN AND FRED H. GAGE

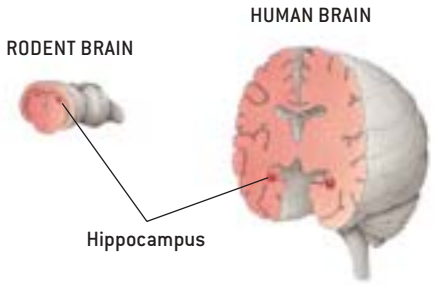
CUT YOUR SKIN, and the wound closes within days. Break a leg, and the fracture will usually mend if the bone is set correctly. Indeed, almost all human tissues can repair themselves to some extent throughout life. Remarkable stem cells account for much of this activity. These versatile cells resemble those of a developing embryo in their ability to multiply almost endlessly and to generate not only carbon copies of themselves but also many different kinds of cells. The versions in bone marrow offer a dramatic example. They can give rise to all the cells in the blood: red ones, platelets and a panoply of white types. Other stem cells yield the various constituents of the skin, the liver or the intestinal lining.

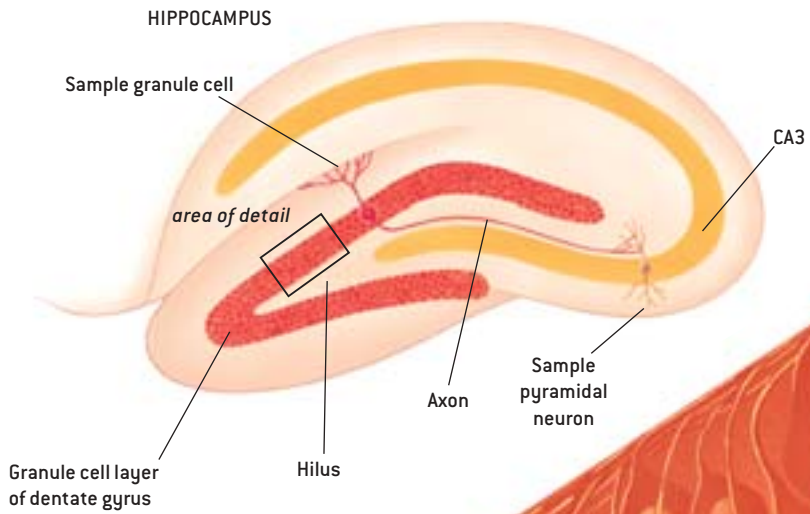
The brain of the adult human can sometimes compensate for damage quite well, by making new connections among surviving nerve cells (neurons). But it cannot repair itself, because it lacks the stem cells that would allow for neuronal regeneration. That, anyway, is what most neurobiologists firmly believed until quite recently.

In November 1998 Peter S. Eriksson of Sahlgrenska University Hospital in Göteborg, Sweden, along with one of us (Gage) at the Salk Institute for Biological Studies in San Diego and several colleagues, published the startling news that the mature human brain does spawn neurons routinely in at least one site—the hippocampus, an area important to memory and learning. (The hippocampus is not where memories are stored, but it helps to form them after receiving input from other brain regions. People with hippocampal damage have difficulty acquiring knowledge yet can recall information learned before their injury.)

The absolute number of new cells is low relative to the total number in the brain. Nevertheless, considered with recent findings in animals, our discovery

TOMO NARASHIMA





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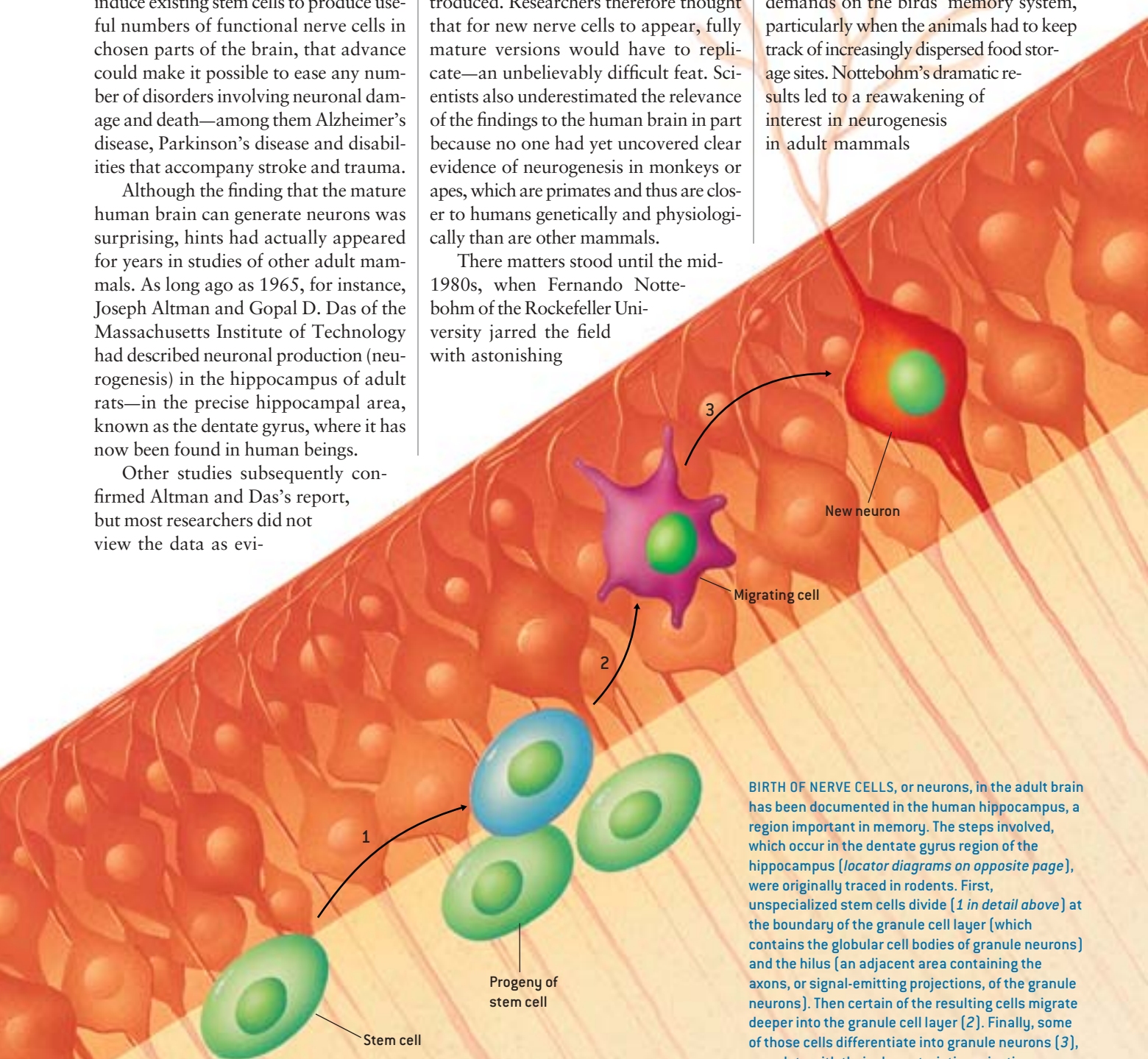
raises some tantalizing prospects for medicine. Current data suggest that stem cells probably make new neurons in another part of the human brain and also reside, albeit dormantly, in additional locations. Hence, the adult brain, which repairs itself so poorly, might actually harbor great potential for neuronal regeneration. If investigators can learn how to induce existing stem cells to produce useful numbers of functional nerve cells in chosen parts of the brain, that advance could make it possible to ease any number of disorders involving neuronal damage and death—among them Alzheimer's disease, Parkinson's disease and disabilities that accompany stroke and trauma.

Although the finding that the mature human brain can generate neurons was surprising, hints had actually appeared for years in studies of other adult mammals. As long ago as 1965, for instance, Joseph Altman and Gopal D. Das of the Massachusetts Institute of Technology had described neuronal production (neurogenesis) in the hippocampus of adult rats—in the precise hippocampal area, known as the dentate gyrus, where it has now been found in human beings.

Other studies subsequently confirmed Altman and Das's report, but most researchers did not view the data as evidence of significant neurogenesis in adult mammals or as an indication that the human brain might have some regenerative potential. One reason was that the methods then available could neither estimate accurately the number of neurons being born nor prove definitively that the new cells were neurons. Further, the concept of brain stem cells had not yet been introduced. Researchers therefore thought that for new nerve cells to appear, fully mature versions would have to replicate—an unbelievably difficult feat. Scientists also underestimated the relevance of the findings to the human brain in part because no one had yet uncovered clear evidence of neurogenesis in monkeys or apes, which are primates and thus are closer to humans genetically and physiologically than are other mammals.

There matters stood until the mid-1980s, when Fernando Nottebohm of the Rockefeller University jarred the field with astonishing results in adult canaries. He discovered that neurogenesis occurred in brain centers responsible for song learning and, moreover, that the process accelerated during the seasons in which the adult birds acquired their songs. Nottebohm and his co-workers also showed that neuron formation in the hippocampus of adult chickadees rose during seasons that placed high demands on the birds' memory system, particularly when the animals had to keep track of increasingly dispersed food storage sites. Nottebohm's dramatic results led to a reawakening of interest in neurogenesis in adult mammals



BIRTH OF NERVE CELLS, or neurons, in the adult brain has been documented in the human hippocampus, a region important in memory. The steps involved, which occur in the dentate gyrus region of the hippocampus (*locator diagrams on opposite page*), were originally traced in rodents. First, unspecialized stem cells divide (*1 in detail above*) at the boundary of the granule cell layer (which contains the globular cell bodies of granule neurons) and the hilus (an adjacent area containing the axons, or signal-emitting projections, of the granule neurons). Then certain of the resulting cells migrate deeper into the granule cell layer (*2*). Finally, some of those cells differentiate into granule neurons (*3*), complete with their characteristic projections.

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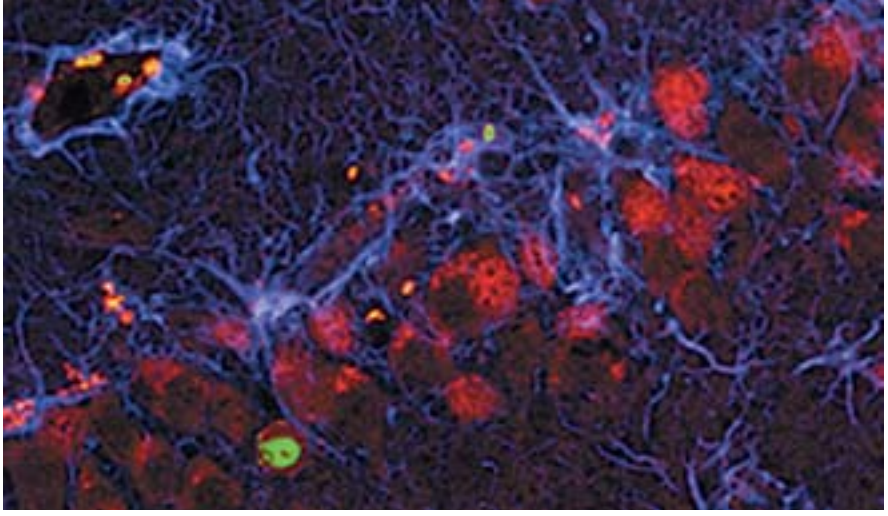

PROOF OF NEURON FORMATION in the mature human brain includes this micrograph of hippocampal tissue (*above*) from an adult who died of cancer. Neurons are marked in red. The green in a neuron reveals that the cells' chromosomes harbor a substance—bromodeoxyuridine (BrdU)—that was injected into a number of the patients to assess tumor growth. BrdU becomes integrated into the DNA of dividing cells (such as stem cells) but is not retained by already established neurons. Its presence therefore signals that the marked cells differentiated into neurons only after the BrdU was delivered.

and caused investigators to ponder once more whether the mature human brain had regenerative potential.

Optimism about the possibility of human neurogenesis was short-lived, however. At about the same time, Pasko Rakic and his associates at Yale University pioneered the study of neurogenesis in adult primates. That work, which was well done for its time, failed to find new brain neurons in grown rhesus monkeys.

Logic, too, continued to argue against neuronal birth in the adult human brain. Biologists knew that the extent of neurogenesis had become increasingly restricted throughout evolution, as the brain became more complex. Whereas lizards and other lower animals enjoy massive neuronal regeneration when their brains are damaged, mammals lack that robust response. It seemed reasonable to assume that the addition of neurons to the intricately wired human brain would threaten the orderly flow of signals along established pathways.

Signs that this reasoning might be flawed emerged only a few years ago. First, a team headed by Elizabeth Gould and Bruce S. McEwen of Rockefeller and Eberhard Fuchs of the German Primate Center in Göttingen revealed in 1997 that some neurogenesis occurs in the hippocampus of the primatelike tree shrew. Then, in March 1998, they found the same phenomenon in the marmoset. Marmoset monkeys are evolutionarily more distant from humans than rhesus monkeys, but they are nonetheless primates.

Studies in Humans

CLEARLY, THE QUESTION of whether humans possess a capacity for neurogenesis in adulthood could be resolved only by studying people directly. Yet such studies seemed impossible, because the methods applied to demonstrate new neuron formation in animals did not appear to be transferable to people.

Those techniques vary but usually take advantage of the fact that before cells divide, they duplicate their chromosomes, which enables each daughter cell to receive a full set. In the animal experiments, investigators typically inject subjects with a traceable material (a "marker") that will become integrated only into the DNA of cells preparing to divide. That marker becomes a part of the DNA in the resulting daughter cells and is then inherited by the daughters' daughters and by future descendants of the original dividing cells.

After a while, some of the marked cells differentiate—that is, they specialize, becoming specific kinds of neurons or glia (the other main class of cells in the brain). Having allowed time for differentiation to occur, workers remove the brain and cut it into thin sections. The sections are stained for the presence of neurons and glia and are viewed under a microscope. Cells that retain the marker (a sign of their derivation from the original dividing cells) and also have the anatomic and chemical characteristics of neurons can be assumed to have differentiated into nerve cells after the marker was introduced into the body. Fully differentiated neurons do not divide and cannot integrate the marker; they therefore show no signs of it.

Living humans obviously cannot be examined in this way. That obstacle seemed insurmountable until Eriksson hit on a solution during a sabbatical with our group at Salk. A clinician, he one day found himself on call with a cancer specialist. As the two chatted, Eriksson learned that the substance we had been using as our marker for dividing cells in animals—bromodeoxyuridine (BrdU)—was coincidentally being given to some terminally ill patients with cancer of the tongue or larynx. These patients were part of a study that involved injecting the compound to monitor tumor growth.

Eriksson realized that if he could obtain the hippocampus of study participants who eventually died, analyses conducted at Salk could identify the neurons and see whether any of them displayed the DNA marker. The presence of BrdU would mean the affected neurons had formed after that substance was delivered. In other words, the study could prove that neurogenesis had occurred, presumably through stem cell proliferation and differentiation, during the patients' adulthood.

Eriksson obtained the patients' consent to investigate their brains after death. Between early 1996 and February 1998, he raced to the hospital and was given

THE AUTHORS

GERD KEMPERMANN and FRED H. GAGE have worked together since 1995, when Kempermann began a three-year term as a postdoctoral fellow in Gage's laboratory at the Salk Institute for Biological Studies in San Diego. Kempermann, who holds a medical degree from the University of Freiburg in Germany, is now assistant professor at Max Delbrück Center for Molecular Medicine in Berlin. Gage has been professor in the Laboratory of Genetics at Salk since 1995 and professor in the department of neurosciences at the University of California, San Diego, since 1988. He earned his doctorate from Johns Hopkins University in 1976 and was associate professor of histology at Lund University in Sweden before moving to California.

LINDA KITABAYASHI *Salk Institute*

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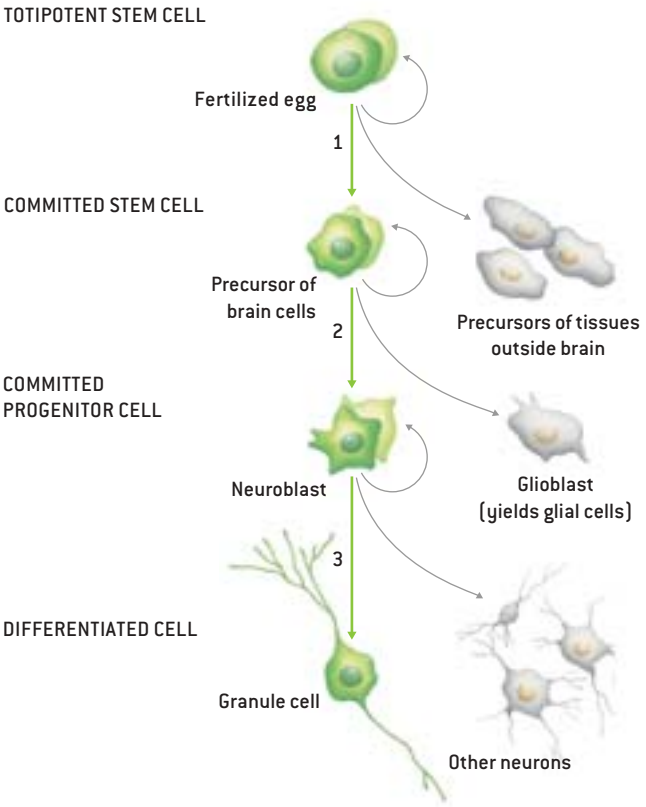
brain tissue from five such patients between the ages of 57 and 72 who had passed away. As hoped, all five brains displayed new neurons—specifically those known as granule cells—in the dentate gyrus. These patients donated their brains to this cause, and we owe this proof of adult human neurogenesis to their generosity. Since this time Gage and his colleagues, as well as Steven A. Goldman and his associates at Cornell University Medical College, have isolated brain cells from autopsies and biopsies of the adult human hippocampus. We have shown that these cells can divide in culture dishes and can be induced to give rise to neurons, confirming the capacity for neurogenesis in the adult human brain.

Do the New Neurons Work?

OF COURSE the mere demonstration of human neurogenesis is not enough. If the ultimate goal is to stimulate controlled neuronal regeneration in ailing human brains, scientists will want to determine the locations of stem cells capable of evolving into neurons. They will also need to be sure that neurons derived from such cells will be functional and able to send and receive messages appropriately. Fortunately, the discovery that neurogenesis in the rodent hippocampus does, after all, mirror activity in the human brain means that investigators can return to studies in rats and mice to seek clues.

Past work in rodents has revealed that some neurogenesis occurs throughout life not only in the hippocampus but in the brain's olfactory system as well. Stem cells also reside in such brain regions as the septum (involved in emotion and learning) and the striatum (involved in fine-tuning motor activity) and in the spinal cord. The cells outside the hippocampus and olfactory system do not appear to produce new neurons under normal conditions, though.

If the front part of the animal's brain were transparent, the dentate gyrus portion of the hippocampus would be seen as a thin, dark layer, roughly the shape of a sideways V [*see diagrams on pages 38 and 39*]. This V consists of the cell bodies of granule neurons—the globular parts that contain the nucleus. An adjacent layer inside the V is called the hilus. It is composed primarily of the axons, or long signal-carrying projections, through which granule cells relay signals to a hippocampal relay station known as CA3.



GRANULE CELL DEVELOPMENT in an embryo is thought to occur through the steps shown in green. A totipotent stem cell, able to give rise to any cell in the body, produces early descendants that include still unspecialized stem cells committed to producing cells of the brain (*1*). These committed cells later yield "progenitor" cells destined to make only neurons (*2*) or only glial cells (which promote neuronal survival). Ultimately, neuronal progenitors spawn granule cells in the hippocampus (*3*) or other kinds of neurons elsewhere in the brain. Steps 2 and 3 now appear to recur throughout life in the human hippocampus.

The stem cells that give rise to newly born granule cells sit at the boundary of the dentate gyrus and the hilus. These cells divide continuously. Many of the progeny are exactly like their parents, and a large number apparently die soon after being produced. But some migrate deeper into the granule cell layer and assume the appearance of the surrounding granule cells, complete with multiple projections for receiving and sending signals. They also extend their axons along the same tracts used by their already established neighbors.

The stem cells that yield new neurons in the olfactory system line the walls of fluid-filled brain cavities known as lateral ventricles. Arturo Alvarez-Buylla of Rockefeller and his co-workers have demonstrated that certain descendants of these stem cells migrate a good distance into the olfactory bulb, where they take on the characteristic features of neurons in that area.

Given that the new neurons in both brain regions look like their earlier-born counterparts, chances are good that they behave like those neurons. But how might this surmise be proved? Studies analyzing the effects of environment on brain anatomy and learning have been instructive.

In the early 1960s Mark R. Rosenzweig and his colleagues at the University of California at Berkeley removed rodents from their standard, rather spartan laboratory conditions and put them into an enriched environment, where they luxuriated in very large cages and shared the company of many other rodents. They could also explore their surroundings (which were continually changed by the caretakers), take spins in running wheels and play with a variety of toys.

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Rosenzweig's group and later that of William T. Greenough of the University of Illinois described amazing consequences of living under such improved conditions. Relative to animals kept in standard cages, those enjoying the high life ended up with slightly heavier brains, greater thickness in certain brain structures, differences in the levels of some neurotransmitters (the molecules that carry stimulatory or inhibitory messages from one neuron to another), more connections between nerve cells and increased branching of neuronal projections. Moreover, they performed better on learning tests; for instance, they were more successful at learning to navigate mazes.

Together the various results implied that the environmental changes had led to improved brain function. Since then, neurobiologists have become convinced that enriching the environment of mature rodents influences brain wiring in ways that enhance brainpower. For years, however, they dismissed the notion that the production of new nerve cells in the adult brain could contribute to such improvements, even though Altman suggested as early as 1964 that such a process should be considered.

Additional findings have confirmed that environmental manipulations do affect adult neurogenesis. Applying technology not available in the 1960s, our group demonstrated in 1997 that adult mice given enriched living conditions grew 60 percent more new granule cells in the dentate gyrus than did genetically identical control animals. They also did better on a learning task that involved finding their way out of a pool of water. Enrichment even enhanced neurogenesis and learning performance in very old mice, which have a base rate of neuronal production that is much lower than that in younger adults.

We do not claim that the new neurons are solely responsible for the behavioral improvements, because changes in wiring configurations and in the chemical microenvironment in the involved brain areas surely play an important part. On the other hand, it would be very surprising if such a dramatic jump in neuron formation, as well as the preservation of adult neurogenesis throughout evolution, served no function.

Hunt for Controls

A PLETHORA of articles has described individual factors that, if manipulated, affect adult neurogenesis. These manipulations ranged from trauma and stroke to models of epilepsy and the application of antidepressant drugs. Despite the great number of studies undertaken, based on many different experimental paradigms and using different analytical criteria, no clear picture of how adult neurogenesis is regulated has yet emerged. The range of effective factors and the apparent subtle differences in their effects, however, suggest that adult neurogenesis in general is very sensitive to changes in many regulatory systems of the brain. It seems that there are some aspects of adult neurogenesis that react to stimuli in a rather nonspecific way, while others react more specifically. The race is on to find the specific factors that will control adult neurogenesis. We are particularly interested in how the activity-dependent regulation of adult neurogenesis is mediated at the level of molecules and genes.

An understanding of the controls on neuron formation could eventually teach neurobiologists how to prompt such regeneration where it is needed. Aside from environmental enrichment, various other factors that influence neurogenesis have been identified in animal studies over the past several years.

These results will make the most sense if readers recall that neurogenesis has many steps—from stem cell proliferation, to selected survival of some progeny, to migration and differentiation. It turns out that factors influencing one step along the way may not affect others. An increase in stem cell proliferation can yield a net rise in new neurons if the rates of daughter cell survival and differentiation remain constant, but the neuronal number may not rise if the survival and differentiation rates change in opposite directions. Similarly, neurons will be added if proliferation stays constant but survival and differentiation increase.

Among the regulatory influences that have been uncovered are some that usually seem to discourage neurogenesis. In the past few years, for example, Gould and McEwen have reported that certain everyday inputs into the dentate gyrus may actually keep a lid on nerve cell production. Specifically, neurotransmitters that stimulate granule cells to fire will also inhibit stem cell proliferation in the hippocampus. High levels of glucocorticoid hormones in the blood inhibit adult neurogenesis as well.

Despite the many studies undertaken, no clear picture of how adult neurogenesis is regulated has emerged.

Given these findings, it is perhaps no surprise that the team has shown stress to reduce stem cell proliferation in the same region. Stress leads to the release of excitatory neurotransmitters in the brain and to the secretion of glucocorticoid hormones from the adrenals. Understanding inhibition is important for learning how to overcome it. But that aspect of the picture is still far from clear. For instance, the discovery that extreme levels of excitatory transmitters and of certain hormones can constrain neurogenesis does not necessarily mean that lower levels are detrimental; in fact, they may be helpful.

As for factors that promote hippocampal neurogenesis, we and others have been trying to identify which features of an enriched environment have the strongest effect. With her associates, Gould, now at Princeton University, showed that participation in a learning task, even in the absence of enriched living, enhances the survival of the cells generated by stem cell division, resulting in a net elevation in the number of new neurons.

Meanwhile our group compared neurogenesis in two groups of mice kept in standard cages, one with a running wheel and one without. The mice having unlimited access to the wheels made heavy use

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of the opportunity and ended up with twice as many new nerve cells as their sedentary counterparts did, a figure comparable to that found in mice placed in an enriched environment. In the runners, a higher rate of stem cell division was involved in the final effect, whereas it played no role in the gains of the enriched-living group. In the latter case (as in Gould's study), stimulating conditions apparently promoted survival of stem cell progeny, so that more of those cells lived to become neurons. This finding highlighted once again that the processes regulating neurogenesis in adults are complex and occur on several levels.

Certain molecules are known to influence neurogenesis. We and our co-workers have evaluated epidermal growth factor and fibroblast growth factor, which despite their names have been shown to affect nerve cell development in cell cultures. With H. Georg Kuhn, then at Salk, and Jürgen Winkler, then at the University of California at San Diego, we delivered these compounds into the lateral ventricles of adult rats, where they evoked striking proliferation by the resident stem cells. Epidermal growth factor favored differentiation of the resulting cells into glia in the olfactory bulb, but fibroblast growth factor promoted neuronal production.

Interestingly, the induction of certain pathological conditions, such as epileptic seizures or stroke, in adult animals can evoke dramatic stem cell division and even neurogenesis. Whether the brain can make use of this response to replace needed neurons is not known. In the case of the seizures, aberrant connections formed by newborn neurons may be part of the problem. The stem cell division and neurogenesis are more evidence that the brain harbors potential for self-repair. The question is, why does that potential usually go unused?

In the experiments discussed so far, we and others examined regulatory events by holding genes constant: we observed the neurological responses of genetically identical (inbred) animals to different inputs. Another way to uncover controls on neurogenesis is to hold the environment constant and compare genes in strains of animals that differ innately in their rates of neuron production. Presumably, the genes that vary include those affecting the development of new nerve cells. In a similar approach, researchers can compare the genes active in brain regions that display neurogenesis and in brain regions that do not. Genetic studies are under way.

ENRICHED LIVING ENVIRONMENT (*above*) is far superior to standard laboratory conditions for stimulating neurogenesis in the dentate gyrus of the mouse hippocampus. Scientists are trying to determine which aspects of the richer environment exert the strongest effect. New findings comparing animals living in standard cages with and without a running wheel suggest that increased running could have an important role.

Genes serve as the blueprints for proteins, which in turn carry out the bulk of cellular activities, such as inducing cell division, migration or differentiation. Therefore, if the genes participating in neuronal generation can be identified, investigators should be able to discover their protein products and to tease out the precise contributions of the genes and their proteins to neurogenesis.

Repairing the Brain

WITH CONTINUED DILIGENCE, scientists may eventually be able to trace the molecular cascades that lead from a specific stimulus—be it an environmental cue or some internal event—to particular alterations in genetic activity that prompt rises or falls in neurogenesis. Then they will have much of the information needed to induce neuronal regeneration at will. Such a therapeutic approach could involve administration of key regulatory molecules or other pharmacological agents, delivery of gene therapy to supply helpful molecules, transplantation of stem cells, modulation of environmental or cognitive stimuli, alterations in physical activity, or some combination of these factors.

Compilation of such techniques could take decades. Once collected, though, they might be applied in several ways. They might provide some level of repair, both in brain areas known to manifest some neurogenesis and in sites where stem cells exist but are normally quiescent. Doctors might also be able to stimulate stem cells to migrate into areas where they usually do not go and to mature into the specific kinds of nerve cells required by a given patient. Although the new cells would not regrow whole brain parts or restore lost memories, they could, for example, manufacture valuable amounts of dopamine (the neurotransmitter whose depletion is responsible for the symptoms of Parkinson's) or other substances.

Research in related areas of science will contribute to the search for these advanced therapeutic approaches. For instance, several laboratories have learned to culture human embryonic stem cells—highly versatile cells, derived from early embryos, that are capable of giving rise to virtually any cell type in the human body. One day it might be possible to prod these embryonic stem cells into generating offspring that are committed to becoming a selected type of neuron. Such cells might then be transplanted into damaged sites to replenish lost nerve cells.

Transplants may, of course, be rejected by a recipient's immune system. Scien-

JAMES ARONOVSKY

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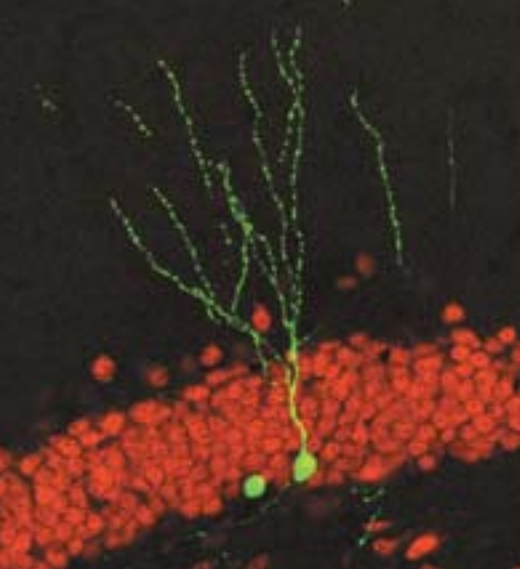

NEW NEURONS, born in the dentate gyrus, were labeled with a retrovirus that expressed green fluorescent protein (GFP). Because GFP is expressed in living cells, these newly born cells can be proved to be functional.

tists are exploring many ways around that problem. One solution could be to harvest stem cells from the brains of the affected patients themselves and to manipulate that material instead of stem cells from a donor. Researchers have devised relatively noninvasive ways of extracting such brain cells from patients.

These medical applications are admittedly goals and are nowhere close to reality at the moment. Indeed, the challenges ahead are huge. Notably, at one point or another analyses of the controls on neurogenesis and of proposed therapies for brain disorders will have to move from rodents to people. To study humans without interfering with their health, researchers will have to make use of extremely clever protocols, such as ones involving the noninvasive imaging techniques known as functional magnetic resonance imaging (fMRI) or positron emission tomography (PET). Further, we must develop safeguards ensuring that neurons stimulated to form in the human brain (or transplanted into it) will do just what we want them to do and will not interfere with normal brain function.

The Role of Neurogenesis

THE MAIN QUESTION remains: What is the functional use of adult neurogenesis? The apparent complexity of regulation and the responsiveness to functional stimuli are highly suggestive of a meaningful role for neurogenesis in hippocampal function. Henriette van Praag of Salk and Alejandro F. Schinder, now at the University of California at San Diego, and one of us (Gage) developed a new method to label living, newly born cells [*see micrograph at left*] and recently succeeded in demonstrating that the electrophysiological properties of the newly generated hippocampal neurons are identical to those of the neighboring older cells. This finding answered the urgent question of whether adult neurogenesis produces functional neurons. The role that these new functional neurons play in the hippocampus, however, remains to be established.

Attempts to link neurogenesis to learning and memory have been made, but the results are inconclusive. The hippocampus is generally considered to be the gateway to memory. It processes information before long-term storage in the cortical areas. This process is called the consolidation of memory. We postulate that the function of new neurons must be linked to this process. The new cells, however, are not added to the hippocampus as a "memory chip." Their number would be too low to store any meaningful amount of information. Also, information is stored in the strength of the connections in a network of neurons, not in individual cells. We further postulate that new neurons are added strategically to the processing network in the dentate gyrus. They could be new gatekeepers at the portal to memory, modifying the processor according to increasing functional needs. This theory has yet to be proved, however.

One question that needs to be clarified is whether neurogenesis takes place in additional areas of the brain. The hippocampus and the olfactory system are the two regions of the adult brain in which adult neurogenesis has been described. A great controversy has arisen over the question of whether there is neurogenesis outside of these classical neurogenic regions. Although Gould's group reported new neurons in surprisingly high numbers in the neocortex, this finding was convincingly disputed by David Kornack of the University of Rochester and by Pasko Rakic, who after careful microscopic analysis could not find new cortical neurons.

From cell culture studies in rodents it is known that neuronal stem cells that can produce neurons in a petri dish can be derived from practically all brain regions, including the cortex. Under physiological conditions, however, no new neurons seem to develop from these cells as long as they are in the brain and outside of the two classical neurogenic regions. Jeffrey D. Macklis and his colleagues at Harvard University have demonstrated that, under the condition of highly specific and circumscribed damage to individual neurons in the cortex of mice, these cells can be replaced by natural, or endogenous, progenitor cells. This finding cannot be easily applied to more general conditions, but it shows that cortical neurogenesis is possible in principle.

How can the neurogenic potential of neural stem cells in the adult brain be tapped for therapeutic purposes? It might one day turn out that targeted neurogenesis is indeed an option for neurological disorders. Many questions remain unanswered, but with growing interest in this area, potential may meet reality sooner rather than later. Furthermore, the expected benefits of unlocking the brain's regenerative potential will justify all the effort that will be required. SA

MORE TO EXPLORE

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HENRIETTE VAN PRAAG *Salk Institute for Biological Studies*

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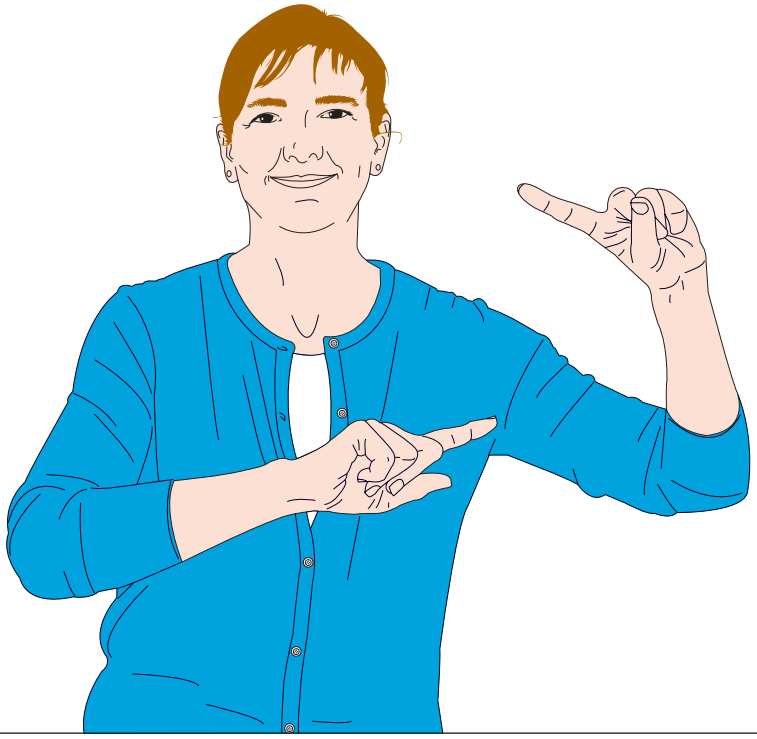

HOW DOES THE HUMAN BRAIN PROCESS LANGUAGE? NEW STUDIES OF DEAF SIGNERS HINT AT AN ANSWER

ONE OF THE GREAT MYSTERIES of the human brain is how it understands and produces language. Until recently, most of the research on this subject had been based on the study of spoken languages: English, French, German and the like. Starting in the mid-19th century, scientists made large strides in identifying the regions of the brain involved in speech. For example, in 1861 French neurologist Paul Broca discovered that patients who could understand spoken language but had difficulty speaking tended to have damage to a part of the brain's left hemisphere that became known as Broca's area. And in 1874 German physician Carl Wernicke found that patients with fluent speech but severe comprehension problems typically had damage to another part of the left hemisphere, which was dubbed Wernicke's area.

Similar damage to the brain's right hemisphere only very rarely results in such language disruptions, which are called aphasias. Instead right hemisphere damage is more often associated with severe visual-spatial problems, such as the inability to copy a simple line drawing. For these reasons, the left hemisphere is often branded the verbal hemisphere and the right hemisphere the spatial hemisphere. Although this dichotomy is an oversimplification, it does capture some of the main clinical differences between individuals with damage to the left side of the brain and those with damage to the right.

But many puzzles remain. One that has been particularly hard to crack is why language sets up shop where it does. The locations of Wernicke's and Broca's areas seem to make sense: Wernicke's area, involved in speech comprehension, is located near the auditory cortex, the part of the brain that receives signals from the ears. Broca's area, involved in speech production, is located next to the part of the motor cortex that controls the muscles of the mouth and lips [*see illustration on page 48*]. But is the brain's organization for language truly based on the functions of hearing and speaking?

One way to explore this question is to study a language that uses different sensory and motor channels. Reading and writing, of course, employ vision for comprehension and hand movements for expression, but for most people these activities depend, at least in part, on brain systems involved in the use of a spoken language. The sign languages of the deaf, however, precisely fit the bill. Over the past two decades, we have ex-

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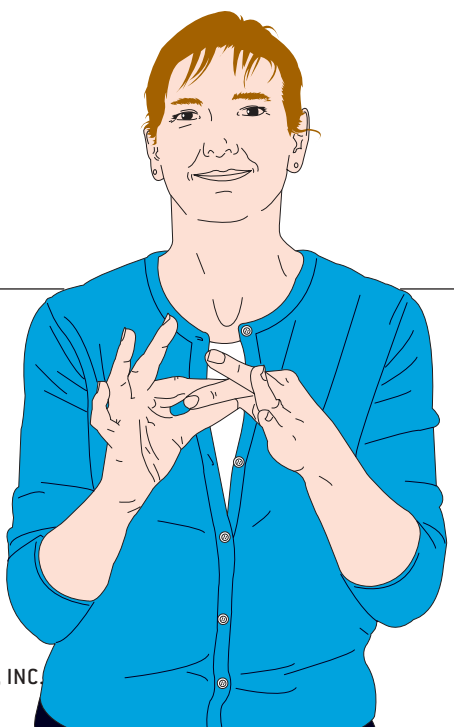
SIGN language in the BRAIN

by Gregory Hickok, Ursula Bellugi and Edward S. Klima



Illustrations by Peter Stemler

TRANSLATION of the phrase "sign language in the brain" into American Sign Language is shown in these artist's renderings, which are based on photographs of a deaf signer.

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amined groups of deaf signers who have suffered damage to either the right or the left hemisphere of their brains, mostly as a result of strokes. By evaluating their proficiency at understanding and producing signs, we set out to determine whether the brain regions that interpret and generate sign language are the same ones involved in spoken language. The surprising results have illuminated the workings of the human brain and may help neurologists treat the ills of their deaf patients.

The Signs of Language

MANY PEOPLE MISTAKENLY BELIEVE that sign language is just a loose collection of pantomime-like gestures thrown together willy-nilly to allow rudimentary communication. But in truth, sign languages are highly structured linguistic systems with all the grammatical complexity of spoken languages. Just as English and Italian have elaborate rules for forming words and sentences, sign languages have rules for individual signs and signed sentences. Contrary to another common misconception, there is no universal sign language. Deaf people in different countries use very different sign languages. In fact, a deaf signer who acquires a second sign language as an adult will actually sign with a foreign accent! Moreover, sign languages are not simply manual versions of the spoken languages that are used in their surrounding communities. American Sign Language (ASL) and British Sign Language, for example, are mutually incomprehensible.

Sign and spoken languages share the abstract properties of language but differ radically in their outward form. Spoken languages are encoded in acoustic-temporal changes—variations in sound over time. Sign languages, however, rely on visual-spatial changes to signal linguistic contrasts [*see box on opposite page*]. How does this difference in form affect the neural organization of language? One might hypothesize that sign language would be supported by systems in the brain's right hemisphere because signs are visual-spatial signals. Accordingly, one could contend that the sign-language analogue of Wernicke's area in deaf signers would be near the brain regions associated with visual processing and that the analogue of Broca's area would be near the motor cortex controlling hand and arm movements.

When we began to test this hypothesis in the 1980s, two fundamental questions needed to be answered: Did deaf signers with brain damage have sign-language deficits? And if so, did the deficits resemble either Wernicke's aphasia (comprehension problems and error-prone speech) or Broca's aphasia (good comprehension but difficulty in producing fluent speech)? The answer to both questions was a resounding yes. One of the first patients studied by our group signed fluently, using all the proper grammatical markers of ASL, but the message conveyed by his signing was often incoherent. An English gloss of one of his utterances reads:

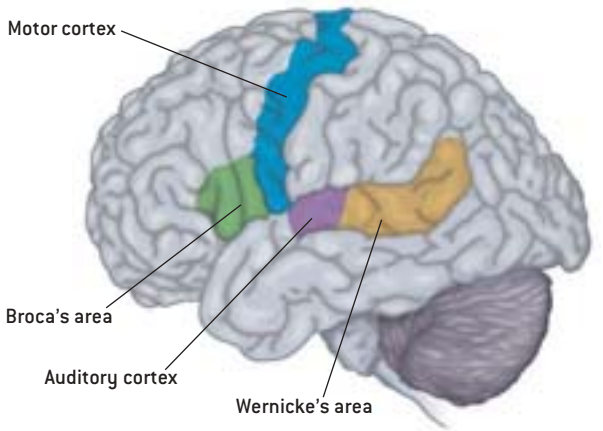
> And there's one (way down at the end) [unintelligible]. The man walked over to see the (disconnected), an extension of the (earth) room. It's there for the man (can live) a roof and light with shades to (keep pulling down).

The patient's disorganized signing and apparent lack of comprehension of others' signs were very similar to the symptoms of hearing patients with Wernicke's aphasia. Another deaf patient we studied early in the research program had extreme difficulty producing signs. She had to struggle to shape and orient her hands to perform the proper movement for virtually every sign she attempted. Most of her utterances were limited to isolated signs. This was not merely a motor control problem: when asked to copy line drawings of objects such as an elephant or a flower, she did so accurately. Also, in contrast to her severe sign-language production problems, her comprehension of sign language was excellent. This profile of language abilities parallels the symptoms of Broca's aphasia.

But where was the brain damage that caused these sign aphasias? The answer was surprising. Both patients had lesions in their left hemispheres. And the lesions were located just about where you'd expect to find them in hearing patients with similar problems. The deaf signer with comprehension diffi-

Where Language Lives

TWO OF THE REGIONS of the brain's left hemisphere that play important roles in language processing are Broca's area and Wernicke's area (there are several others). Broca's area is activated in hearing individuals when they are speaking and in deaf people when they are signing. Wernicke's area is involved in the comprehension of both speech and signs.



THE AUTHORS

GREGORY HICKOK, URSULA BELLUGI and *EDWARD S. KLIMA* have worked together on sign language aphasia for a decade. Hickok is associate professor in the department of cognitive sciences at the University of California, Irvine, and director of the Laboratory for Cognitive Brain Research, where he studies the functional anatomy of language. Bellugi is director of the Salk Institute's Laboratory for Cognitive Neuroscience in La Jolla, Calif., where she conducts research on language and its biological foundations. Much of her research is in collaboration with Klima, who is professor emeritus at the University of California, San Diego, and a co-director of Salk.

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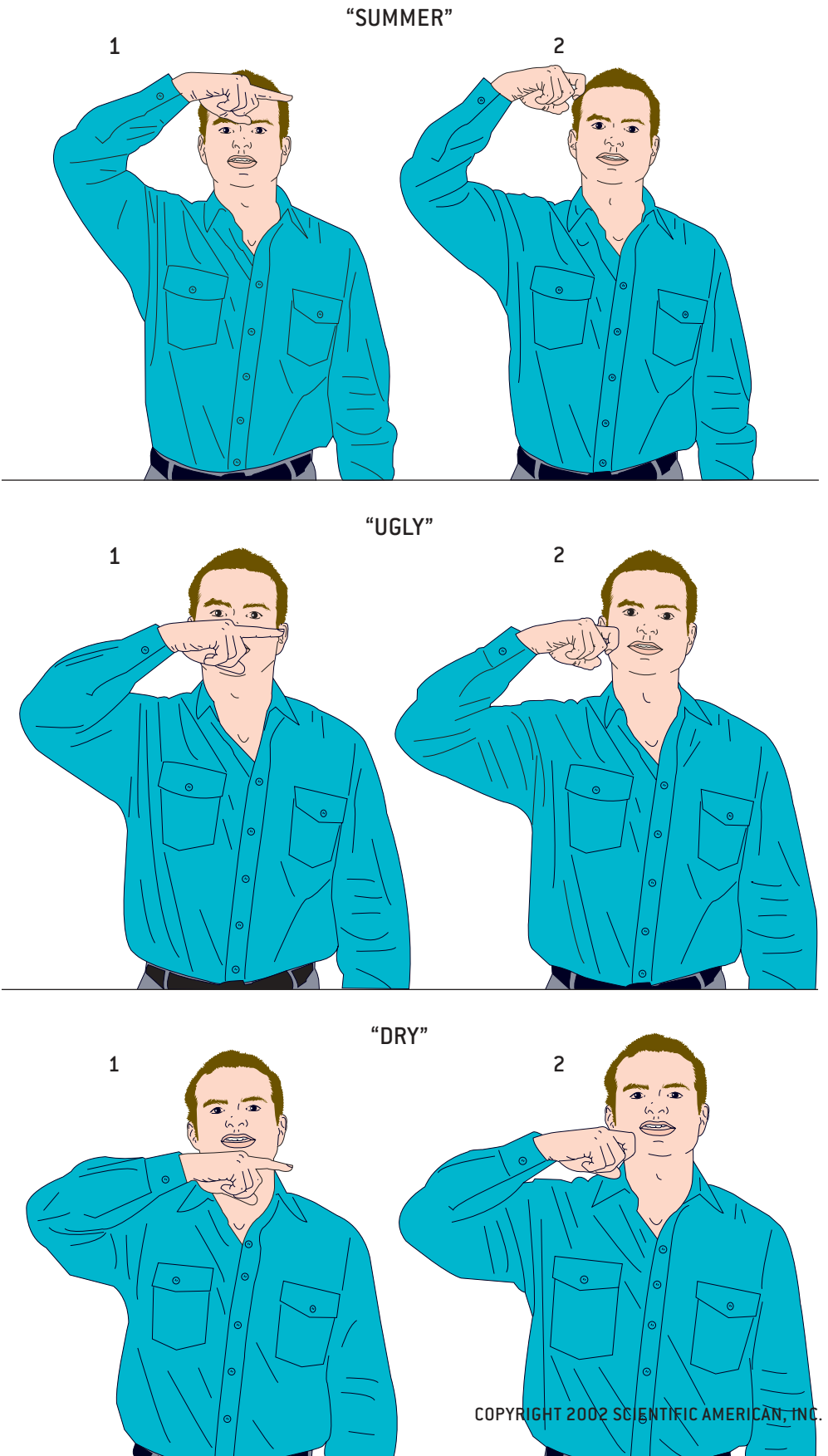
THE BUILDING BLOCKS OF SIGN LANGUAGE



SIGN LANGUAGES, like spoken languages, have several kinds of linguistic structure, including phonological, morphological and syntactic levels. At the phonological level, signs are made up of a small set of components, just as spoken words are composed of a small set of consonants and vowels. The components of signs include hand shapes, the locations around the body where signs are made, the movements of the hands and arms, and the orientation of the hands (for example, palm up versus palm down). In American Sign Language (ASL) the signs for "summer," "ugly" and "dry" have the same hand shape, movement and orientation but differ in location [*see illustrations at left*]. Likewise, signs such as "train," "tape" and "chair" share hand shape, orientation and location but differ in movement.

At the morphological level, ASL has grammatical markers that systematically change the meaning of signs. Morphological markers in English include fragments like "-ed," which can be added to most verbs to indicate past tense ("walk" becomes "walked"). Whereas in English the markers are added to the beginning or end of a word, in ASL the signs are modified using distinctive spatial patterns. For example, adding a rolling movement to the sign "give" (and to most ASL verb signs) changes the sign's meaning to "give continuously." Signers can use different patterns to modify the verb to mean "give to all," "give to each," "give to each other" and many other variations.

At the syntactic level, ASL specifies the grammatical relations among signs (that is, who is doing what to whom) in ways that do not occur in spoken languages. In English the order of the words provides the primary cue for the syntactic organization of a sentence such as "Mary criticized John." Reverse the order of the nouns, and you reverse the meaning of the sentence. Signers of ASL can use word-order cues as well, but they need not. Instead signers can point to a distinct position in space while signing a noun, thus linking the word with that position. Then the signer can move the verb sign from Mary's position to John's to mean "Mary criticized John" and in the other direction to mean the reverse.

LOCATION of a sign is a critical element in conveying meaning. In American Sign Language, "summer" is articulated near the forehead, "ugly" near the nose and "dry" near the chin.

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COMMON PROBLEM experienced by left hemisphere–damaged (LHD) deaf signers is the production of paraphasias—slips of the hand—analogous to the slips of the tongue experienced by LHD hearing patients. The illustration at the right shows the correct form of the sign for "fine," whereas the drawing on the opposite page shows an error often made by LHD signers. In the latter figure, the signer articulated the location and movement of the sign correctly but used the wrong hand shape, resulting in something that has no meaning in ASL—a nonsense sign, equivalent to "bline" or "gine" in English.

Although the hand shape in this paraphasia is incorrect for "fine," it is used in many other ASL signs, such as "play" and "California." Similar paraphasias include errors in producing the proper location, movement and hand orientation of a sign, as well as mistakes in rendering the morphological and syntactic structure of the language.

CORRECT SIGN FOR "FINE"

The brain's left hemisphere is dominant for sign language, just as it is for speech.

culties had damage that included Wernicke's area, whereas the patient who had trouble making signs had damage that involved Broca's area.

These observations showed that the left hemisphere plays a crucial role in supporting sign language. But what about the right hemisphere? One would think that damage to the right hemisphere, which appears to be critically involved in many visual-spatial functions, would have a devastating effect on sign-language ability as well. But this assumption is apparently wrong. Signers with damage to the right hemisphere were fluent and accurate in their production of signs, used normal grammar and comprehended signs with ease. This held true even in patients whose nonlinguistic visual-spatial abilities had been severely compromised by their brain damage. One signer with damage to the right hemisphere, for example, could not create or copy recognizable drawings and failed to notice objects in the left part of his visual field (a condition known as hemispatial neglect). Yet he could communicate very efficiently in sign language.

Subsequent research using larger groups of deaf signers confirmed the early case studies. A study published by our team in 1996 compared the sign-language abilities of 13 left hemisphere–damaged (LHD) signers with those of 10 right hemisphere–damaged (RHD) signers. As a group, the LHD signers performed poorly across a wide range of sign-language measures: They had trouble comprehending isolated signs and signed sentences and were likely to have problems with fluency as well. They also had difficulty with picture-naming tasks and frequently made paraphasic errors—slips of the hand—in which they inadvertently substituted one sign for another or one component of a sign, such as hand shape, for another. In contrast, the RHD signers performed well on all these tasks. The study also showed that difficulties with sign-language fluency were not caused by more general problems in controlling voluntary hand or arm movements: patients who had trouble making signs were often capable of producing nonmeaningful hand and arm gestures.

We obtained similar results in another study, this one focusing on sign-language comprehension in 19 lifelong signers with brain lesions, 11 with damage to the left hemisphere and eight with damage to the right. The LHD group performed significantly worse than the RHD group on three tests that evaluated their understanding of single signs, simple sentences and complex sentences. The most impaired signers were those with damage to the brain's left temporal lobe, where Wernicke's area is located.

Taken together, these findings suggest that the brain's left hemisphere is dominant for sign language, just as it is for speech. The organization of the brain for language does not appear to be particularly affected by the way in which language is perceived and produced.

The Story Gets Complicated

AS WE NOTED at the beginning of this article, the assumed left-right dichotomy of the brain—with verbal abilities concentrated in the left hemisphere and visual-spatial abilities clus-

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tered in the right—is an oversimplification. Research over the past few decades has shown that most cognitive abilities can be divided into multiple processing steps. At some levels, brain activity may be lateralized (taking place primarily in one hemisphere), whereas at others the activity may be bilateral (occurring in both).

Language ability, for instance, has many components. A hearing person must be able to perceive and produce individual speech sounds and the words they make up; otherwise, one could not distinguish "cup" from "pup." In addition, one must be able to recognize morphological additions ("walking" vs. "walked"), syntactic constructions ("the dog chased the cat" vs. "the dog was chased by the cat"), and melodic intonations ("the *White* House" vs. "the white *house*"). Finally, to conduct an extended discourse one must be able to establish and maintain a coherent connection between characters and events over the course of many sentences.

Of all these aspects of linguistic ability, the production of language is the one most sharply restricted to the brain's left hemisphere. Damage to the left hemisphere often interferes with the ability to select and assemble appropriate sounds and words when speaking. Right hemisphere damage rarely does. One exception to the left hemisphere's monopoly on language production is the creation of a coherent discourse. Patients with right hemisphere damage may be able to construct words and sentences quite well, but they frequently ramble from one subject to the next with only a loose thread of a connection between topics.

The perception and comprehension of language appear to be less confined to the left hemisphere than language production is. Both hemispheres are capable of distinguishing individual speech sounds, and the right hemisphere seems to have a role in the comprehension of extended discourse. But deciphering the meaning of words and sentences seems to take place primarily in the left hemisphere. This may explain why language was originally considered to be the exclusive province of the left hemisphere: the most common tests for aphasia evaluated the comprehension and production of words and sentences, not longer discourses.

Nonlinguistic spatial abilities can also be broken down into components with differing patterns of lateralization. Although the most severe impairments of spatial abilities occur more commonly following damage to the right hemisphere (both in deaf and hearing populations), researchers have observed some visual-spatial deficits in LHD hearing people. The symptoms typically involve difficulties in perceiving or reproducing the local-level features of a visual stimulus—such as the details in a drawing—even though the LHD patients can correctly identify or reproduce the drawing's overall configuration. RHD hearing people tend to show the opposite pattern. Thus, it has been suggested that the left hemisphere is important for local-level spatial perception and manipulation, whereas the right hemisphere is important for global-level processes.

This more sophisticated picture of the brain raises an interesting question: Is the division of visual-spatial abilities between the two hemispheres—local level in the left, global level in the right—related to the division of sign-language abilities? Individual signs and signed sentences can be thought of as pieces of the language, whereas an extended discourse can represent how those pieces are put together. Perhaps the left hemisphere is dominant for producing and comprehending signs and signed sentences because those processes are dependent on local-level spatial abilities. And perhaps the right hemisphere is dominant for establishing and maintaining a coherent discourse in sign language because those processes are dependent on global-level spatial abilities.

INCORRECT SIGN FOR "FINE" TYPICALLY PRODUCED BY A SIGNER WITH LEFT HEMISPHERE DAMAGE

We set out to test this hypothesis. Our research confirmed that many RHD signers have trouble with extended discourse: their narratives are full of tangential utterances and even confabulations—just the kind of difficulties that hearing RHD patients often have. But some RHD signers face another type of problem. Discourse in sign language has a unique spatial organization: when telling a story with many characters, the signer identifies each one using a different location. The space in front of the signer becomes a sort of virtual stage on which each character has his or her own spot. Our studies found that some RHD signers were able to

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The brain is a highly modular organ, with each module organized around a particular computational task.

stay with a topic in their discourse but failed to maintain a consistent spatial framework for the characters in their narratives.

Is either of these types of discourse problems in RHD deaf signers causally connected to deficits in their nonlinguistic spatial abilities? It would appear not. We studied one RHD signer whose spatial abilities were severely impaired yet who had no trouble signing a coherent story. Another RHD patient had only mild visual-spatial problems yet could not sustain a proper spatial framework for the characters in the narrative. Clearly, the cognitive systems in the right hemisphere that support nonlinguistic spatial abilities are different from the ones that support extended discourse.

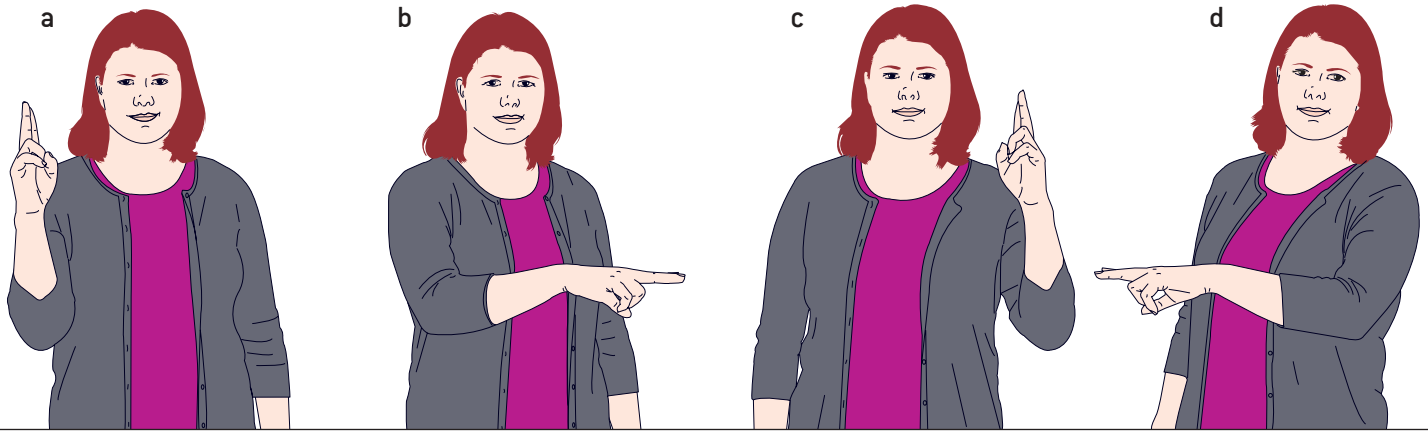
What about deaf signers with damage to the left hemisphere? Are their sign-language aphasias caused by impairments in local-level spatial abilities? To address this issue, we asked a group of deaf signers to reproduce line drawings and hierarchical figures, which have recognizable local and global features. (An example would be the letter "D" fashioned out of a constellation of small "y"s.) Just like hearing patients with left hemisphere damage, the LHD deaf subjects tended to reproduce the global configuration of the drawings correctly but often left out some of the details. (The RHD deaf subjects exhibited the reverse pattern, drawing pictures with lots of detail but a disorganized whole.) We found no correlation between the severity of the local-level spatial deficits in the LHD subjects and the severity of their sign-language aphasias. Contrary to all expectations, the sign-language abilities of lifelong deaf signers appear to be independent of their nonlinguistic spatial skills.

It is possible that we have missed some fine distinctions in the organization of the brain for language in hearing patients and signers. Studies of patients with brain lesions are limited in their precision: to ascertain exactly which parts of the brain are involved in sign language, researchers would need to examine dozens of deaf signers with lesions in just the right places, and it would take decades to find them all. But the introduction of noninvasive brain imaging techniques—functional magnetic resonance imaging (fMRI) and positron-emission tomography (PET)—has given scientists new tools for probing the neural roots of language.

Researchers have employed these techniques to investigate the role of Broca's area in speech and sign production. Imaging results have shown that Broca's area is indeed activated in hearing patients when they are speaking and in deaf patients when they are signing. Brain imaging has also confirmed that the regions that play a role in sign-language comprehension are much the same as those involved in the understanding of spoken language. In one recent study, researchers used fMRI methods to observe the brain activity of lifelong deaf signers who were watching videotapes of sentences in ASL. The investigators found regions of activity in several parts of the left temporal lobe, including parts of Wernicke's area, and in several regions of the left frontal lobe, including Broca's area.

The study also found regions of activity in the right temporal lobe and right frontal lobe. This result has led some researchers to suggest that sign-language comprehension may be more bilaterally organized than spoken-language comprehen-

SEQUENCE OF DRAWINGS below shows the correct maintenance of a spatial framework for an extended discourse in American Sign Language. The signer is describing a series of pictures that show two children painting each other's faces as they sit side by side at a table. At the start of the discourse, the signer linked each child to a particular location in space: Alice on the signer's right and Bob on the signer's left (*not shown*). Subtle shifts in the signer's body position and the direction of the movement of the sign for "paint" (from Alice's location on her right to Bob's location on her left) indicate that Alice is painting Bob (*a, b*). The reverse movements (*c, d*) indicate that Bob is painting Alice.



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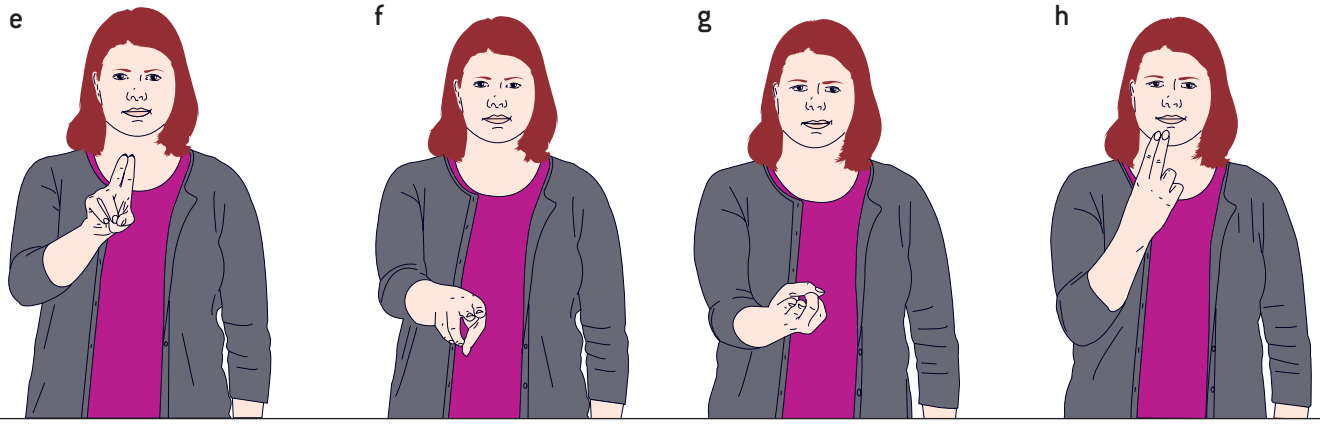

MANY SIGNERS with right hemisphere damage make mistakes in their spatial organization of a discourse. They can correctly link the characters in the narrative to positions in space, but they often fail to reference these positions consistently. In the drawings above, the signer does not link the sign for "paint" to the positions of Alice and Bob. An English equivalent of this lack of specificity might be: "Alice and Bob were sitting at a table, painting. Suddenly someone painted on someone's face (*e, f*), and then someone painted on someone's face (*g, h*)."

sion. But bilateral activity has also been detected in studies of hearing subjects listening to speech. More research is needed to clarify the role of the right hemisphere in sign-language processing. In any case, the studies of brain lesions make it clear that if differences exist between spoken and sign language, they are likely to be subtle and language specific.

Lessons from Sign Language

SIGN LANGUAGE involves both linguistic and visual-spatial processing—two abilities that are supported by largely distinct neural systems in hearing individuals. But contrary to all expectations, the neural organization of sign language has more in common with that of spoken language than it does with the brain organization for visual-spatial processing. Why should this be the case?

The answer suggested by our line of research, as well as the work of others, is that the brain is a highly modular organ, with each module organized around a particular computational task. According to this view, the processing of visual-spatial information is not confined to a single region of the brain. Instead different neural modules process visual inputs in different ways. For example, visual inputs that carry linguistic information would be translated into a format optimized for linguistic processing, allowing the brain to access the meanings of signs, extract grammatical relations, and so on. But visual stimuli that carry a different kind of information—such as the features and contours of a drawing—would be translated into a format that is optimized for, say, carrying out motor commands to reproduce that drawing. The computational demands of these two kinds of processing tasks are very different, and thus different neural systems are involved.

Viewed in this way, it is not so surprising that comprehending and producing sign language appear to be completely independent of visual-spatial abilities such as copying a drawing. Although they both involve visual inputs and manual outputs, the tasks are different in fundamental ways. Consequently, we would expect them to share brain systems to some extent at the peripheral levels of processing—for instance, at the primary visual cortex that receives signals from the optic nerve—but to diverge in more central, higher-level brain systems.

The situation with spoken and sign languages is just the opposite. These two systems differ radically in their inputs and outputs but appear to involve very similar linguistic computations. We therefore expect that spoken and sign languages will share a great deal of neural territory at the more central, higher-level brain systems but diverge at the more peripheral levels of processing. At the sensory end, for example, the peripheral processing of speech occurs in the auditory cortices in both hemispheres, whereas the initial processing of signs takes place in the visual cortex. But after the first stages of processing, the signals appear to be routed to central linguistic systems that have a common neural organization in speakers and signers.

These findings may prove useful to neurologists treating deaf signers who have suffered strokes. The prognosis for the recovery of the signers' language abilities will most likely be similar to that of hearing patients with the same brain damage. Furthermore, when neurosurgeons remove brain tumors from deaf signers, they must take the same precautions to avoid damaging the language centers as they do with hearing patients.

A major challenge for future research will be to determine where the peripheral processing stages leave off and the central stages begin (or even if there is such a sharp boundary between the two). More study is also needed to understand the nature of the computations carried out at the various levels of linguistic processing. The similarities and differences between spoken and sign languages are ideally suited to answering these questions. SA

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Dreams may be crucial in mammalian memory processing. Important information acquired while awake may be reprocessed during sleep

The Meaning of Dreams

By Jonathan Winson

Throughout history, human beings have sought to understand the meaning of dreams.

The ancient Egyptians believed dreams possessed oracular power—in the Bible, for example, Joseph's elucidation of Pharaoh's dream averted seven years of famine. Other cultures have interpreted dreams as inspirational, curative or alternative reality. During the past century, scientists have offered conflicting psychological and neuroscientific explanations for dreams. In 1900, with the publication of *The Interpretation of Dreams,* Sigmund Freud proposed that dreams were the "royal road" to the unconscious, that they revealed in disguised form the deepest elements of an individual's inner life.

More recently, in contrast, dreams have been characterized as meaningless, the result of random nerve cell activity. Dreaming has also been viewed as the means by which the brain rids itself of unnecessary information—a process of "reverse learning," or unlearning.

Based on recent findings in my own and other neuroscientific laboratories, I propose that dreams are indeed meaningful. Studies of the hippocampus (a brain structure crucial to memory), of rapid eye movement (REM) sleep and of a brain wave called theta rhythm suggest that dreaming reflects a pivotal aspect of the processing of memory. In particular, studies of theta rhythm in subprimate animals have provided an evolutionary clue to the meaning of dreams. They appear to be the nightly record of a basic mammalian memory process: the means by which animals form strategies for survival and evaluate current experience in light of those strategies. The existence of this process may explain the meaning of dreams in human beings.

Stages of Sleep and Dreaming

THE PHYSIOLOGY OF DREAMING was first understood in 1953, when researchers characterized the human sleep cycle. They found that sleep in humans is initiated by the hypnogogic state, a period of several minutes when thoughts consist of fragmented images or minidramas. The hypnogogic state is followed by slow-wave sleep, so called because at that time the brain waves of the neocortex (the convoluted outer mantle of the brain) are low in frequency and large in amplitude. These signals are measured as electroencephalographic (EEG) recordings.

Researchers also discovered that a night's sleep is punctuated by periods in which the EEG readings are irregular in frequency and low in amplitude—similar to those observed in awake individuals. These periods of mental activity are called REM sleep. Dreaming takes place solely during these periods. While in REM sleep, motor neurons are inhibited, preventing the body from moving freely but allowing extremities to remain slightly active. Eyes move rapidly in unison under closed lids, breathing becomes irregular, and heart rate increases.

The first REM stage of the night follows 90 minutes of slow-wave sleep and lasts for 10 minutes. The second and third REM periods follow shorter slow-wave sleep episodes but grow progressively longer themselves. The fourth and final REM interval lasts 20 to 30 minutes and is followed by awakening. If a dream is remembered at all, it is most often the one that occurred in this last phase of REM sleep.

This sleep cycle—alternating slow-wave and REM sleep—appears to be present in all placental and marsupial mammals. Mammals exhibit the various REM-associated characteristics observed in humans, including EEG readings similar to those of the awake state. Animals also dream. By destroying neurons in the brain stem that inhibit movement during sleep, researchers found that sleeping cats rose up and attacked or were startled by invisible objects—ostensibly images from dreams.

By studying nonprimate animals, scientists have discovered additional neurophysiological aspects of REM sleep. They de-

Updated from the November 1990 issue

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JACOB'S LADDER, painted in 1973 by Marc Chagall, depicts a biblical story. Jacob dreams of angels ascending to and descending from heaven on a ladder.

termined that neural control of this stage of the sleep cycle is centered in the brain stem (the brain region closest to the spinal cord) and that during REM sleep neural signals—called pontine-geniculate-occipital (PGO) cortex spikes—proceed from the brain stem to the center of visual processing, the visual cortex. Brain stem neurons also initiate a sinusoidal wave (one resembling a sine curve) in the hippocampus. This brain signal is called theta rhythm.

At least one animal experiences slow-wave but not REM sleep—and, consequently, does not exhibit theta rhythm when asleep. This animal is the echidna, or spiny anteater, an egg-laying mammal (called a monotreme) that provides some insight into the origin of dreaming. The absence of REM sleep in the echidna suggests that this stage of the sleep cycle evolved some 140 million years ago, when marsupials and placentals diverged from the monotreme line. (Monotremes were the first mammals to develop from reptiles.)

By all evolutionary criteria, the perpetuation of a complex brain process such as REM sleep indicates that it serves an important function for the survival of mammalian species. Understanding that function might reveal the meaning of dreams.

When Freud wrote *The Interpretation of Dreams*, the physiology of sleep was unknown. In light of the discovery of REM sleep, certain elements of his psychoanalytic theory were modified, and the stage was set for more neurologically based theories. Dreaming came to be understood as part of a biologically determined sleep cycle. Yet the central concept of Freud's theory—namely, the belief that dreams reveal a censored representation of our innermost unconscious feelings and concerns—continues to be used in psychoanalysis.

Some theorists abandoned Freud altogether following the neurological discoveries. In 1977 J. Allan Hobson and Robert McCarley of Harvard Medical School proposed the "activation-synthesis" hypothesis. They suggested that dreaming consists of associations and memories elicited from the forebrain (the neocortex and associated structures) in response to random signals from the brain stem such as PGO spikes. Dreams were merely the "best fit" the forebrain could provide to this random bombardment from the brain stem. Although dreams might at times appear to have psychological content, their bizarreness was inherently meaningless.

The sense, or plot, of dreams resulted from order that was imposed on the chaos of neural signals, Hobson said. "That order is a function of our own personal view of the world, our remote memories," he wrote. In other words, the individual's

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emotional vocabulary could be relevant to dreams. In a further revision of the original hypothesis, Hobson also suggested that brain stem activation may serve merely to switch from one dream episode to another.

Reverse Learning

ALTHOUGH HOBSON and McCarley had presented an explanation of dream content, the basic function of REM sleep remained unknown. In 1983 Francis Crick of the Salk Institute for Biological Studies in San Diego and Graeme Mitchison of the University of Cambridge proposed the idea of reverse learning. Working from the Hobson-McCarley assumption of random neocortical bombardment by PGO waves and their own knowledge of the behavior of stimulated neural networks, Crick and Mitchison postulated that a complex associational neural network such as the neocortex might become overloaded by vast amounts of incoming information. The neocortex could then develop false, or "parasitic," thoughts that would jeopardize the true and orderly storage of memory.

According to their hypothesis, REM sleep served to erase these spurious associations on a regular basis. Random PGO waves impinged on the neocortex, resulting in erasure, or unlearning, of the false information. This process served an essential function: it allowed the orderly processing of memory. In humans, dreams were a running record of these parasitic thoughts—material to be purged from memory. "We dream to forget," Crick and Mitchison wrote.

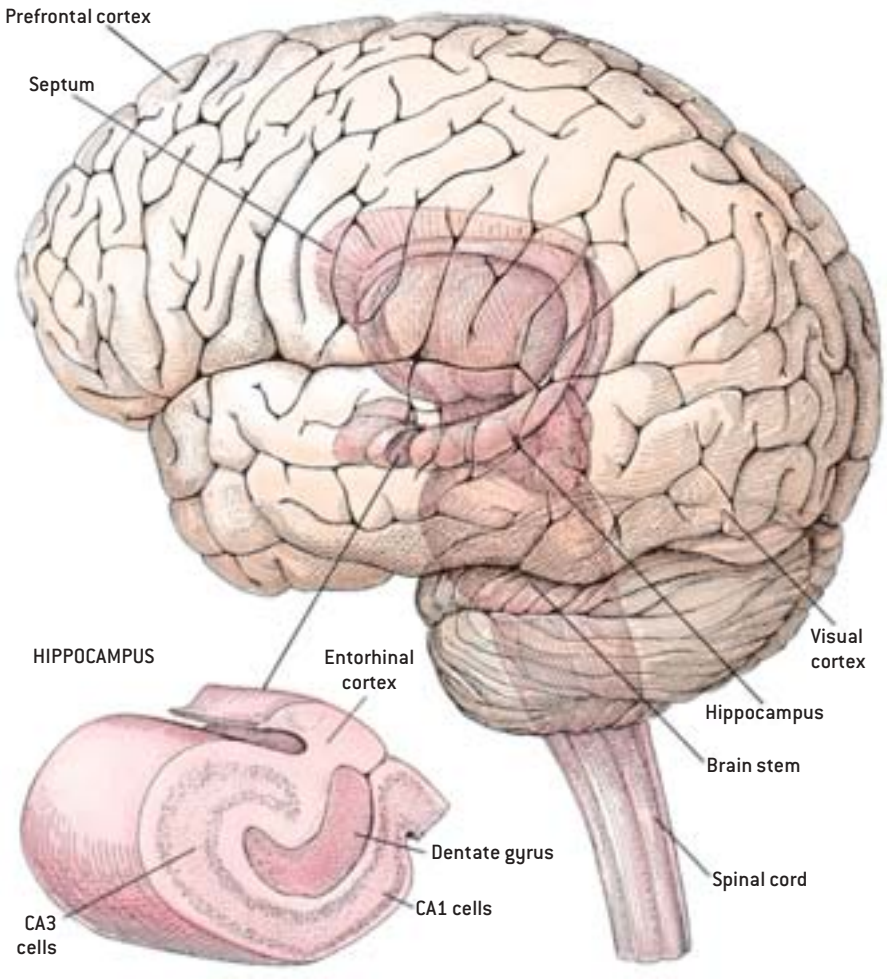
The two researchers proposed a revision in 1986. Erasure of parasitic thoughts accounted only for bizarre dream content. Nothing could be said about dream narrative. Furthermore, dreaming to forget, they said, was better expressed as dreaming to reduce fantasy or obsession.

None of these hypotheses seems to explain adequately the function of dreaming. On the one hand, Freud's theory lacked physiological evidence. (Although Freud had originally intended to describe the neurology of the unconscious and of dreams in his proposed "Project for a Scientific Psychology," the undertaking was premature, and he limited himself to psychoanalysis.) On the other hand, despite revisions to incorporate elements of psychology, most of the later theories denied that dreams had meaning.

Exploring the neuroscientific aspects of REM sleep and of memory processing seemed to me to hold the greatest potential for understanding the meaning and function of dreams. The key to this research was theta rhythm.

Theta rhythm was discovered in 1954 in awake animals by John D. Green and Arnaldo A. Arduini of the University of California at Los Angeles. The researchers observed a regular sinusoidal signal of six cycles per second in the hippocampus of rabbits when the animals were apprehensive of stimuli in their environment. They named the signal theta rhythm after a previously discovered EEG component of the same frequency.

Theta rhythm was subsequently recorded in the tree shrew, mole, rat and cat. Although it was consistently observed in awake animals, theta rhythm was correlated with very different behaviors in each species. For example, in marked contrast to the rabbit, environmental stimuli did not induce theta rhythm in the rat. Rats demonstrated theta rhythm only during movement, typically when they explored. In 1969, however, Case H. Vanderwolf of the University of Western Ontario discovered there was one behavior during which the animals he studied,



ANATOMY OF THE BRAIN and cross section of the hippocampus show some of the regions involved in dreaming. In the hippocampus, incoming information is processed sequentially in the dentate gyrus and the CA3 and the CA1 pyramidal cells (so named for their triangular shape). In nonprimate species, the theta rhythm brain wave is generated in the dentate gyrus and the CA1 cells.

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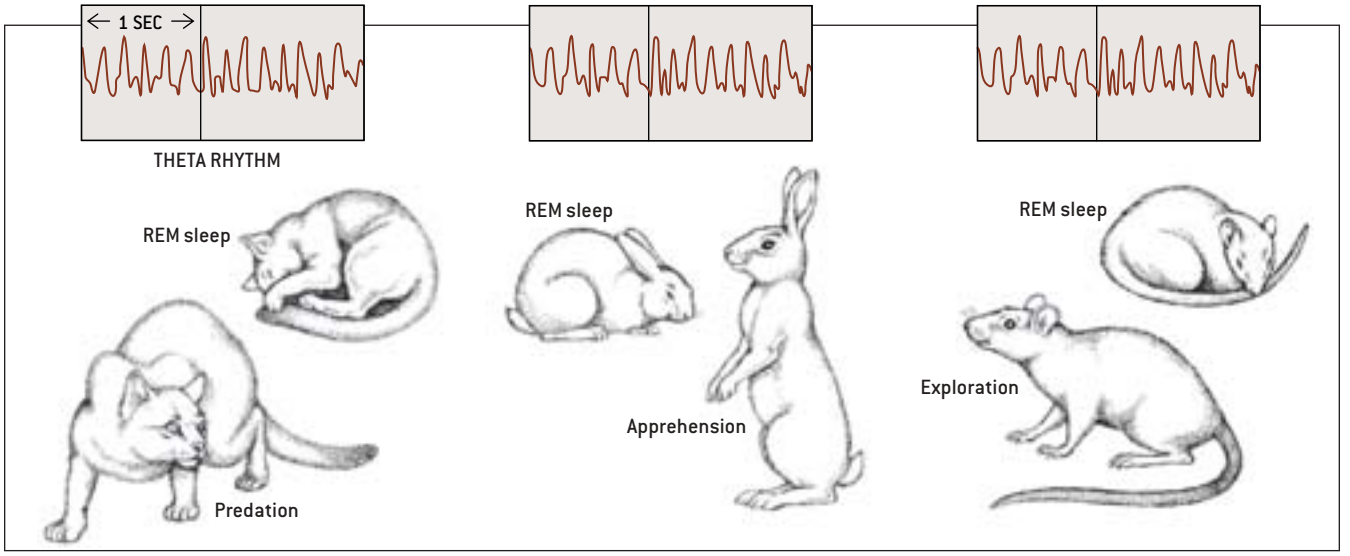

THETA RHYTHM brain signal is present during different waking behaviors in different species. Each of these behaviors is pivotal to the animal's survival. In placental and marsupial animals, theta rhythm is present during rapid eye movement (REM) sleep.

including the rat, showed theta rhythm: REM sleep.

In 1972 I published a commentary pointing out that the different occurrences of theta rhythm could be understood in terms of animal behavior. Awake animals seemed to show theta rhythm when they were behaving in ways most crucial to their survival. In other words, theta rhythm appeared when they exhibited behavior that was not genetically encoded—such as feeding or sexual behavior—but rather a response to changing environmental information. Predatory behavior in the cat, prey behavior in the rabbit, and exploration in the rat are, respectively, most important to their survival. For example, a hungry rat will explore before it eats even if food is placed in front of it.

Role of Theta Rhythm

FURTHERMORE, because the hippocampus is involved in memory processing, the presence of theta rhythm during REM sleep in that region of the brain might be related to that activity. I suggested that the theta rhythm reflected a neural process whereby information essential to the survival of a species—gathered during the day—was reprocessed into memory during REM sleep.

In 1974, by recording signals from the hippocampus of freely moving rats and rabbits, I found the source from which theta rhythm was generated in the hippocampus. Together with the neocortex, the hippocampus is believed to provide the neural basis for memory storage. The hippocampus (from the Greek word for "seahorse," which it resembles in shape) is a sequential structure composed of three types of neurons. Information from all sensory and associational areas of the neocortex converges in a region called the entorhinal cortex; from there it is transmitted to the three successive neuronal populations of the hippocampus. The signal arrives first at the granule cells of the dentate gyrus, then at the CA3 pyramidal cells (so called because of their triangular shape) and finally at the pyramidal cells of CA1. After information is processed by this trio of cells, it is retransmitted to the entorhinal cortex and then back to the neocortex.

My studies showed that theta rhythm was produced in two regions within the hippocampus: the dentate gyrus and the CA1 neurons. The rhythms in these two areas were synchronous. Subsequently, James B. Ranck, Jr., of the State University of New York Downstate Medical Center and his then co-worker Susan Mitchell identified a third synchronous generator in the entorhinal cortex, and Robert Verdes of Wayne State University discovered the brain stem neurons that control theta rhythm. These neurons transmit signals to the septum (a forebrain structure) that activate theta rhythm in the hippocampus and the entorhinal cortex. Thus, the brain stem activates the hippocampus and the neocortex—the core memory system of the brain.

To determine the relation between theta rhythm and memory, I made a lesion in the rat septum. Rats that had previously learned, using spatial cues, to locate a particular position in a maze were no longer able to do so after their septums were disabled. Without theta rhythm, spatial memory was destroyed.

Studies of the cellular changes that bring about memory illustrated the role of theta rhythm. In particular, the discovery in 1973 of long-term potentiation

THE AUTHOR

JONATHAN WINSON started his career as an aeronautical engineer, graduating with an engineering degree from the California Institute of Technology in 1946. He completed his Ph.D. in mathematics at Columbia University and then turned to business for 15 years. Because of his long-standing interest in neuroscience, Winson then began research at the Rockefeller University on memory processing. In 1979 he became associate professor there and continued his work as professor emeritus, retiring in 1996. His research was supported by the National Institute of Mental Health, the National Science Foundation and the Harry F. Guggenheim Foundation.

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(LTP)—a change in neural behavior that reflects previous activity—showed the means by which memory might be encoded. Timothy V. P. Bliss and A. R. Gardner-Medwin of the National Institute of Medical Research in London and Terje Lømo of the University of Oslo found changes in nerve cells that had been intensely stimulated with electrical pulses.

Long-Term Memory Storage

EARLIER STUDIES had shown that if one stimulated the pathway from the entorhinal cortex to the granule cells of the hippocampus, the response of these cells could be measured with a recording electrode. Using this technique, Bliss and his colleagues measured the normal response to a single electrical pulse. Then they applied a long series of high-frequency signals—called tetanic pulses—to this pathway. After the train of tetanic stimuli, a single electrical pulse caused much greater firing in the granule cells than had been observed prior to the experiment. The heightened effect persisted for as long as three days. This phenomenon of LTP was precisely the kind of increase in neuronal strength that could be capable of sustaining memory. LTP is now considered a model for learning and memory.

In a series of experiments, a coherent picture of MEMORY PROCESSING began to emerge.

LTP is achieved by the activity of the NMDA (*N*-methyl-D-aspartate) receptor. This molecule is embedded in the dendrites of the granule cells and the CA1 cells of the hippocampus as well as in neurons throughout the neocortex. Like other neuronal receptors, the NMDA receptor is activated by a neurotransmitter—glutamate in this case. Glutamate momentarily opens a non-NMDA channel in the granule cell dendrite, allowing sodium from the extracellular space to flow into the neuron. This influx causes the granule cell to become depolarized. If the depolarization is sufficient, the granule cell fires, transmitting information to other nerve cells.

Unlike other neuronal receptors, NMDA possesses an additional property. If a further activation of glutamate occurs while the granule cell is depolarized, a second channel opens up, allowing an influx of calcium. Calcium is thought to act as a second messenger, initiating a cascade of intracellular events that culminates in long-lasting synaptic changes—or LTP. (The description given here has been necessarily simplified. LTP is the subject of extensive ongoing investigation.)

Because the tetanic impulses applied by Bliss and his colleagues did not occur naturally in the brain, the question remained as to how LTP was achieved under normal circumstances. In 1986 John Larson and Gary S. Lynch of the University of California at Irvine and Gregory Rose and Thomas V. Dunwiddie of the University of Colorado at Denver suggested that the occurrence of LTP in the hippocampus was linked to theta rhythm. They applied a small number of electrical pulses to CA1 cells in the rat hippocampus and produced LTP, but only when the pulses were separated by the normal time that elapses between two theta waves—approximately 200 milliseconds. Theta rhythm is apparently the natural means by which the NMDA receptor is activated in neurons in the hippocampus.

Work in my laboratory at the Rockefeller University duplicated Larson and Lynch's CA1 findings, but this time in the hippocampal granule cells. Constantine Pavlides, Yoram J. Greenstein and I then demonstrated that LTP was dependent on the presence and phase of theta rhythm. If electrical pulses were applied to the cells at the peak of the theta wave, LTP was induced. But if the same pulse were applied at the trough of the waves—or when theta rhythm was absent—LTP was not induced.

A coherent picture of memory processing was emerging. As a rat explores, for example, brain stem neurons activate theta rhythm. Olfactory input (which in the rat is synchronized with theta rhythm, as is the twitching of whiskers) and other sensory information converge on the entorhinal cortex and the hippocampus. There they are partitioned into 200-millisecond "bites" by theta rhythm. The NMDA receptors, acting in conjunction with theta rhythm, allow for long-term storage of this information.

A similar process occurs during REM sleep. Although there is no incoming information or movement during REM sleep, the neocortical-hippocampal network is once again paced by theta rhythm. Theta rhythm might produce long-lasting changes in memory.

Storing Spatial Memory

THE RESULTS OF ONE of my further experiments served to show that spatial memory was indeed being stored in the rat hippocampus during sleep. John O'Keefe and Jonathan O. Dostrovsky of University College London had demonstrated that individual CA1 neurons in the rat hippocampus fired when the awake animal moved to a particular location—namely, the neuron's place field. The implication of this finding was that the CA1 neuron fired to map the environment, thereby committing it to memory.

In 1989 Pavlides and I located two CA1 neurons in the rat hippocampus that had different place fields. We recorded from both cells simultaneously. After determining the normal firing rates in awake and asleep animals, we positioned a rat in the place field of one of the neurons. The neuron fired vigorously, mapping that location. The second cell fired only sporadically because it was not coding space. We continued recording from the two pairs of neurons as the rat moved about and then entered several sleep cycles. Six pairs of neurons were studied in this manner.

We found that neurons that had coded space fired at a normal rate as the animal moved about prior to sleep. In sleep, however, they fired at a significantly high-

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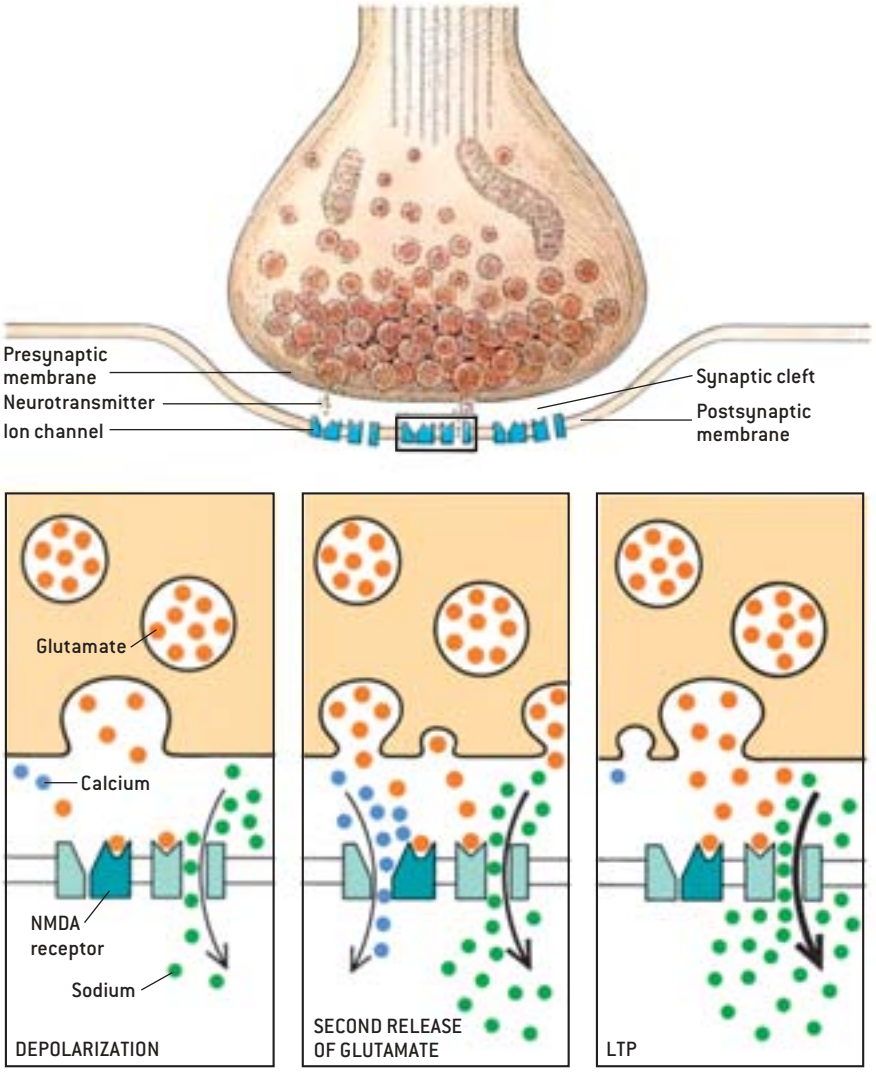

NMDA RECEPTOR activation induces long-term potentiation (LTP), a model for memory. The release of the neurotransmitter glutamate (*left panel*) opens a non-NMDA (*N*-methyl-D-aspartate) receptor channel, allowing the influx of sodium, which depolarizes the neuron. If a further release of glutamate occurs while the cell is depolarized (*center panel*), the NMDA receptor opens a second channel, which allows calcium to flow in, leading to LTP. LTP occurs as a result of increased sodium through the non-NMDA channel (*right panel*) and the subsequent greater depolarization of the cell.

er rate than their previous sleeping baseline. There was no such increase in firing rate during sleep in neurons that had not mapped space. This experiment suggested that the reprocessing or strengthening of information encoded when the animal was awake occurred in sleep at the level of individual neurons.

Bruce L. McNaughton and his colleagues at the University of Arizona have developed a technique for simultaneously recording from a large number of neurons in the hippocampus that map locations. Their technique allows definitive patterns of firing to be identified. In animal studies, they found that ensembles of place-field neurons that code space in the waking state reprocess information during slow-wave sleep and then in REM sleep. These results suggest that sleep processing of memory may have two stages—a preliminary stage in slow-wave sleep and a later phase in REM sleep, when dreaming occurs.

Evolution of REM Sleep

EVIDENCE THAT theta rhythm encodes memories during REM sleep may be derived not only from neuroscientific studies but also from evolution. The emergence of a neural mechanism to process memory in REM sleep suggests differences in brain anatomy between mammals that have that aspect of the sleep cycle and those that do not. And in fact, such differences clearly exist between the echidna and the marsupials and placentals.

The echidna has a large convoluted prefrontal cortex, larger in relation to the rest of the brain than that of any other mammal, even humans. I believe it needed this huge prefrontal cortex to perform a dual function: to react to incoming information in an appropriate manner based on past experience and to evaluate and store new information to aid in future survival. Without theta rhythm during REM sleep, the echidna would not be able to process information while it slept. (The echidna does, however, show theta rhythm when foraging for food.) For higher capabilities to develop, the prefrontal cortex would have to become increasingly large—beyond the capacity of the skull—unless another brain mechanism evolved.

REM sleep could have provided this new mechanism, allowing memory processing to occur "off-line." Coincident with the apparent development of REM sleep in marsupial and placental mammals was a remarkable neuroanatomical change: the prefrontal cortex was dramatically reduced in size. Far less prefrontal cortex was required to process information. That area of the brain could develop to provide advanced perceptual abilities in higher species.

The nature of REM sleep supports this evolutionary argument. During the day, animals gather information that involves locomotion and eye movement. The reprocessing of this information during REM sleep would not be easily separated from the locomotion related to the experience—such disassociation might be expecting too great a revision of brain circuitry. So to maintain sleep, locomotion had to be suppressed by inhibiting motor neurons. Suppressing eye movement was unnecessary because this activity does not disturb sleep.

Eye movement potentials, similar to PGO spikes, accompany rapid eye movement in the waking state and also during REM sleep. The function of these signals has not yet been established, but they may serve to alert the visual cortex to in-

CAROL DONNER (*top*); GABOR KISS (*bottom*)

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coming information when the animal is awake and may reflect the reprocessing of this information during REM sleep. In any case, PGO spikes do not disturb sleep and do not have to be suppressed—unlike motor neurons.

Strategy for Survival

WITH THE EVOLUTION of REM sleep, each species could process the information most important for its survival, such as the location of food or the means of predation or escape—those activities during which theta rhythm is present. In REM sleep this information may be accessed again and integrated with past experience to provide an ongoing strategy for behavior. Although theta rhythm has not yet been demonstrated in primates, including humans, the brain signal provides a clue to the origin of dreaming in humans. Dreams may reflect a memory-processing mechanism inherited from lower species, in which information important for survival is reprocessed during REM sleep. This information may constitute the core of the unconscious.

Dreams MAY REFLECT a memory-processing mechanism inherited from LOWER SPECIES.

Because animals do not possess language, the information they process during REM sleep is necessarily sensory. Consistent with our early mammalian origins, dreams in humans are sensory, primarily visual. Dreams do not take the form of verbal narration.

Also in keeping with the role REM sleep played in processing memories in animals, there is no functional necessity for this material to become conscious. Consciousness arose later in evolution in humans. But neither is there any reason for the material of dreams not to reach consciousness. Therefore, dreams can be remembered—most readily if awakening occurs during or shortly after a REM sleep period.

Consistent with evolution and evidence derived from neuroscience and reports of dreams, I suggest that dreams reflect an individual's strategy for survival. The subjects of dreams are broad-ranging and complex, incorporating self-image, fears, insecurities, strengths, grandiose ideas, sexual orientation, desire, jealousy and love.

Dreams clearly have a deep psychological core. This observation has been reported by psychoanalysts since Freud and is strikingly illustrated by the work of Rosalind Cartwright of Rush-Presbyterian–St. Luke's Hospital in Chicago. Cartwright studied a series of 90 subjects who were undergoing marital separation and divorce. All the subjects were clinically evaluated and psychologically tested to ascertain their attitudes and responses to their personal crisis. Cartwright's subjects were also awakened from REM sleep to report their dreams, which were then interpreted by the subjects themselves without questions that might have influenced their interpretation. In 70 of the individuals studied, the dream content conveyed the person's unconscious thoughts and was strongly correlated with the manner in which he or she was coping with the crisis while awake.

Although the topic "chosen" for consideration during a night's sleep is unpredictable, certain of life's difficulties—as in the case of Cartwright's subjects—so engage psychological survival that they are selected for REM sleep processing. In the ordinary course of events, depending on the individual's personality, the themes of dreams may be freewheeling. Moreover, when joined with the intricate associations that are an intrinsic part of REM sleep processing, the dream's statement may be rather obscure.

Nevertheless, there is every reason to believe that the cognitive process that took place in Cartwright's subjects occurs in every individual. Interpretation of the coherent statement that is being made depends on the individual's tracing of relevant or similar events. These associations are strongly biased toward early childhood experience.

My hypothesis also offers an explanation for the large amount of REM sleep in infants and children. Newborns spend eight hours a day in REM sleep. The sleep cycle is disorganized at this age. Sleep occurs in 50- to 60-minute bouts and begins with REM rather than with slow-wave sleep. By the age of two, REM sleep is reduced to three hours a day, and the adult pattern has been established. Thereafter, the time spent in REM sleep gradually diminishes to a little less than two hours.

REM sleep may perform a special function in infants. A leading theory proposes that it stimulates nerve growth. Whatever the purpose in infants may be, I suggest that at about the age of two, when the hippocampus, which continues to develop after birth, becomes functional, REM sleep takes on its interpretive memory function. The waking information to be integrated at this point in development constitutes the basic cognitive substrate for memory—the concept of the real world against which later experiences must be compared and interpreted. The organization in memory of this extensive infrastructure requires the additional REM sleep time.

For reasons he could not possibly have known, Freud set forth a profound truth in his work. There is an unconscious, and dreams are indeed the "royal road" to understanding it. The characteristics of the unconscious and associated processes of brain functioning, however, are very different from what Freud thought. Rather than being a cauldron of untamed passions and destructive wishes, I propose that the unconscious is a cohesive, continuously active mental structure that takes note of life's experiences and reacts according to its own scheme of interpretation. Dreams are not disguised as a consequence of repression. Their unusual character is a result of the complex associations that are culled from memory.

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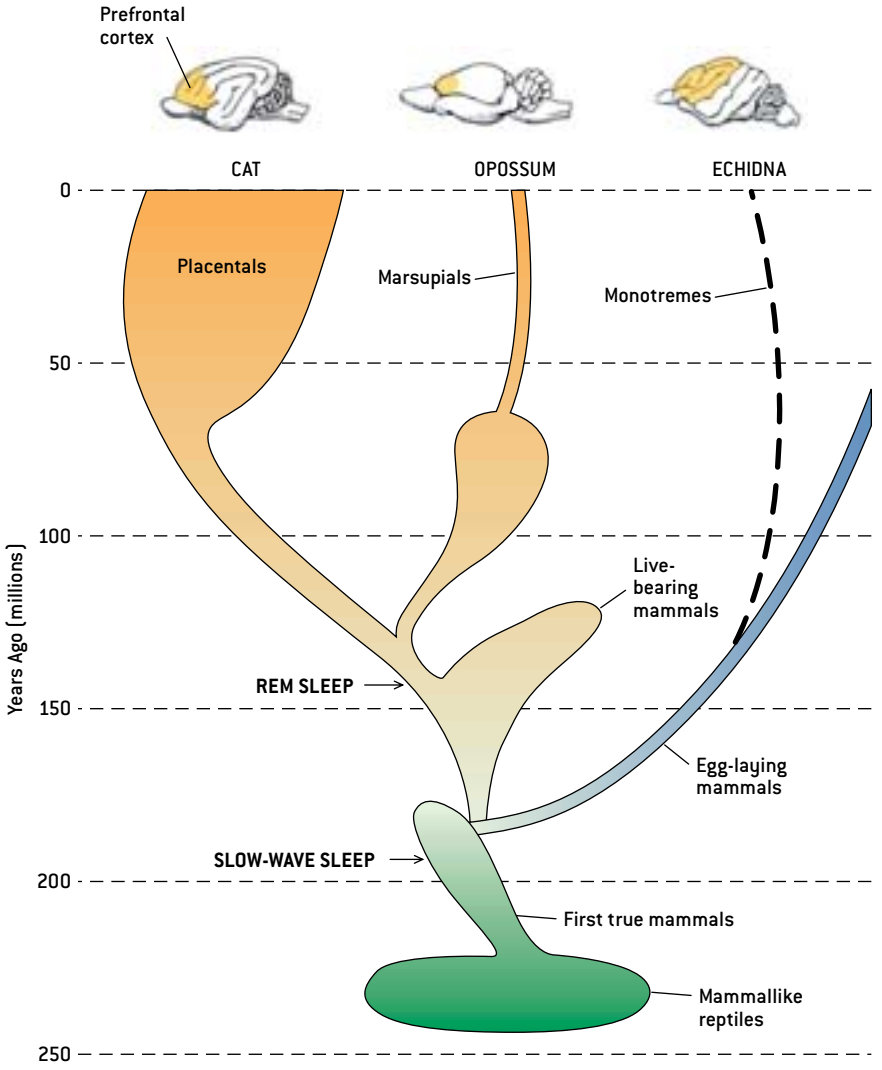

EVOLUTIONARY TREE shows the divergence of placentals and marsupials from monotremes. The echidna, which does not experience REM sleep, has a larger prefrontal cortex compared with the rest of its brain than does any mammal, even humans. It is larger than in similarly sized animals, including the opossum and the cat.

Research on REM sleep suggests that there is a biologically relevant reason for dreaming. The revised version of the Hobson-McCarley activation-synthesis hypothesis acknowledges the deep psychological core of dreams. In its present truncated form, the hypothesis of random brain stem activation has little explanatory or predictive power.

The Crick-Mitchison hypothesis provides a function for REM sleep—reverse learning—but it does not apply to narrative, only to the bizarre elements of the dream. What this implies with regard to REM processing in lower species must be defined before the theory can be evaluated further. In addition, the Crick-Mitchison hypothesis as applied to the hippocampus would suggest that neurons fire randomly during REM sleep, providing reverse learning. Instead, in my experiment on the neurons that coded space, these neurons fired selectively, implying an orderly processing of memory.

Avi Karni and his colleagues at the Weizmann Institute of Science in Israel were able to show that memory processing occurs in humans during REM sleep. In their experiment, individuals learned to identify particular patterns on a screen. The memory of this skill improved after a night with REM sleep. When the subjects were deprived of REM sleep, memory consolidation did not occur. This study opens a promising field for exploration.

Perhaps of greatest interest is evidence supporting the role of REM sleep in memory processing that has emerged from molecular biology. Sidarta Ribeiro and his colleagues at the Rockefeller University have reported that the immediate early gene *zif-268* that is associated with learning is selectively upgraded during REM sleep in rats exposed to experience in a preceding waking period. Further understanding of the role of REM sleep may be expected from this area of research. SA

MORE TO EXPLORE

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Emotion, Memory and the Brain

The neural routes underlying the formation of memories about primitive emotional experiences, such as fear, have been traced

by Joseph E. LeDoux

Despite millennia of preoccupation with every facet of human emotion, we are still far from explaining in a rigorous physiological sense this part of our mental experience. Neuroscientists have, in modern times, been especially concerned with the neural basis of such cognitive processes as perception and memory. They have for the most part ignored the brain's role in emotion. Yet in recent years, interest in this mysterious mental terrain has surged. Catalyzed by breakthroughs in understanding the neural basis of cognition and by an increasingly sophisticated knowledge of the anatomical organization and physiology of the brain, investigators have begun to tackle the problem of emotion.

One quite rewarding area of research has been the inquiry into the relation between memory and emotion. Much of this examination has involved studies of one particular emotion—fear—and the manner in which specific events or stimuli come, through individual learning experiences, to evoke this state. Scientists, myself included, have been able to determine the way in which the brain shapes how we form memories about this basic, but significant, emotional event. We call this process "emotional memory."

By uncovering the neural pathways through which a situation causes a creature to learn about fear, we hope to elucidate the general mechanisms of this form of memory. Because many human mental disorders—including anxiety, phobia, post-traumatic stress syndrome and panic attack—involve malfunctions

Updated from the June 1994 issue

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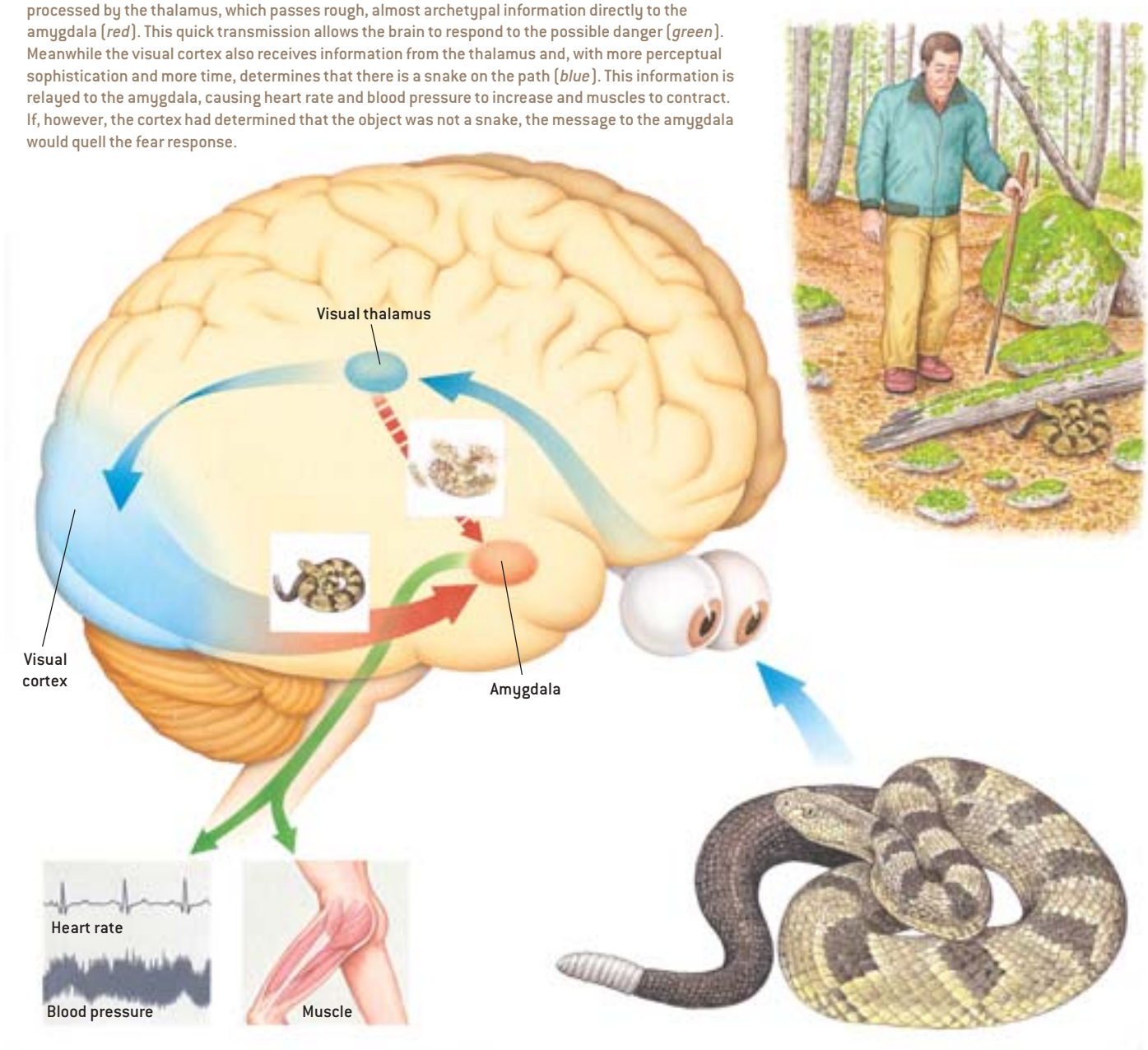
THE FEAR RESPONSE

CORTICAL AND SUBCORTICAL PATHWAYS in the brain—generalized from our knowledge of the auditory system—may bring about a fearful response to a snake on a hiker's path. Visual stimuli are first processed by the thalamus, which passes rough, almost archetypal information directly to the amygdala (*red*). This quick transmission allows the brain to respond to the possible danger (*green*). Meanwhile the visual cortex also receives information from the thalamus and, with more perceptual sophistication and more time, determines that there is a snake on the path (*blue*). This information is relayed to the amygdala, causing heart rate and blood pressure to increase and muscles to contract. If, however, the cortex had determined that the object was not a snake, the message to the amygdala would quell the fear response.



ROBERTO OSTI

in the brain's ability to control fear, studies of the neural basis of this emotion may help us further understand and treat these disturbances.

Most of our knowledge about how the brain links memory and emotion has been gleaned through the study of so-called classical fear conditioning. In this process the subject, usually a rat, hears a noise or sees a flashing light that is paired with a brief, mild electric shock to its feet. After a few such experiences, the rat responds automatically to the sound or light, even in the absence of the shock. Its reactions are typical to any threatening situation: the animal freezes, its blood pressure and heart rate increase, and it startles easily. In the language of such experiments, the noise or flash is a conditioned stimulus, the foot shock is an unconditioned stimulus, and the rat's reaction is a conditioned response, which consists of readily measured behavioral and physiological changes.

Conditioning of this kind happens quickly in rats—indeed, it takes place as rapidly as it does in humans. A single pairing of the shock to the sound or sight can bring on the conditioned effect. Once established, the fearful reaction is relatively permanent. If the noise or light is administered many times without an accompanying electric shock, the rat's response diminishes. This change is called extinction. But considerable evidence suggests that this behavioral alteration is the

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result of the brain's controlling the fear response rather than the elimination of the emotional memory. For example, an apparently extinguished fear response can recover spontaneously or can be reinstated by an irrelevant stressful experience. Similarly, stress can cause the reappearance of phobias in people who have been successfully treated. This resurrection demonstrates that the emotional memory underlying the phobia was rendered dormant rather than erased by treatment.

Fear and Emotional Memory

FEAR CONDITIONING has proved an ideal starting point for studies of emotional memory for several reasons. First, it occurs in nearly every animal group in which it has been examined: fruit flies, snails, birds, lizards, fish, rabbits, rats, monkeys and people. Although no one claims that the mechanisms are precisely the same in all these creatures, it seems clear from studies to date that the pathways are very similar in mammals and possibly in all vertebrates. We therefore are confident in believing that many of the findings in animals apply to humans. In addition, the kinds of stimuli most commonly used in this type of conditioning are not signals that rats—or humans, for that matter—encounter in their daily lives. The novelty and irrelevance of these lights and sounds help to ensure that the animals have not already developed strong emotional reactions to them. So researchers are clearly observing learning and memory at work.

At the same time, such cues do not require complicated cognitive processing from the brain. Consequently, the stimuli permit us to study emotional mechanisms relatively directly. Finally, our extensive knowledge of the neural pathways involved in processing acoustic and visual information serves as an excellent starting point for examining the neurological foundations of fear elicited by such stimuli.

My work has focused on the cerebral roots of learning fear, specifically fear that has been induced in the rat by associating sounds with foot shock. As do most other investigators in the field, I assume that fear conditioning occurs because the shock modifies the way in which neurons in certain important regions of the brain interpret the sound stimulus. These critical neurons are thought to be located in the neural pathway through which the sound elicits the conditioned response.

A decade ago, researchers in my laboratory and others identified major components of this system. Our study began at Cornell University Medical College, where I worked some years ago, when my colleagues and I asked a simple question: Is the auditory cortex required for auditory fear conditioning?

In the auditory pathway, as in other sensory systems, the cortex is the highest level of processing; it is the culmination of a sequence of neural steps that starts with the peripheral sensory receptors, located, in this case, in the ear. If lesions in (or surgical removal of) parts of the auditory cortex interfered with fear conditioning, we could conclude that the region is indeed necessary for this activity. We could also deduce that the next step in the conditioning pathway would be an output from the auditory cortex. But our lesion experiments in rats confirmed what a series of other studies had already suggested: the auditory cortex is not needed in order to learn many things about simple acoustic stimuli.

We then went on to make lesions in the auditory thalamus and auditory midbrain, sites lying below the auditory cortex. Both these areas process auditory signals: the midbrain provides the major input to the thalamus; the thalamus supplies the major input to the cortex. Lesions in both regions eliminated the rat's susceptibility to conditioning. This discovery suggested that a sound stimulus is transmitted through the auditory system to the level of the auditory thalamus but that it does not have to reach the cortex for fear conditioning to occur.

This possibility was somewhat puzzling. We knew that the primary nerve fibers that carry signals from the auditory thalamus extend to the auditory cortex. So David A. Ruggiero, Donald J. Reis and I looked again and found that cells in some regions of the auditory thalamus also give rise to fibers that reach several subcortical locations. Could these neural projections be the connections through which the stimulus elicits the response we identify with fear? We tested this hypothesis by making lesions in each one of the subcortical regions with which these fibers connect. The damage had an effect in only one area: the amygdala.

These findings seemed to place us on the threshold of BEING ABLE TO MAP the entire stimulus response pathway.

Filling in the Picture

THAT OBSERVATION suddenly created a place for our findings in an already accepted picture of emotional processing. For a long time, the amygdala has been considered an important brain region in various forms of emotional behavior. In 1979 Bruce S. Kapp and his colleagues at the University of Vermont reported that lesions in the amygdala's central nucleus interfered with a rabbit's conditioned heart rate response once the animal had been given a shock paired with a sound. The central nucleus connects with areas in the brain stem involved in the control of heart rate, respiration and vasodilation. Kapp's work suggested that the central nucleus was a crucial part of the system through which autonomic conditioned responses are expressed.

In a similar vein, we found that lesions of this nucleus prevented a rat's blood pressure from rising and limited its ability to freeze in the presence of a fear-caus-

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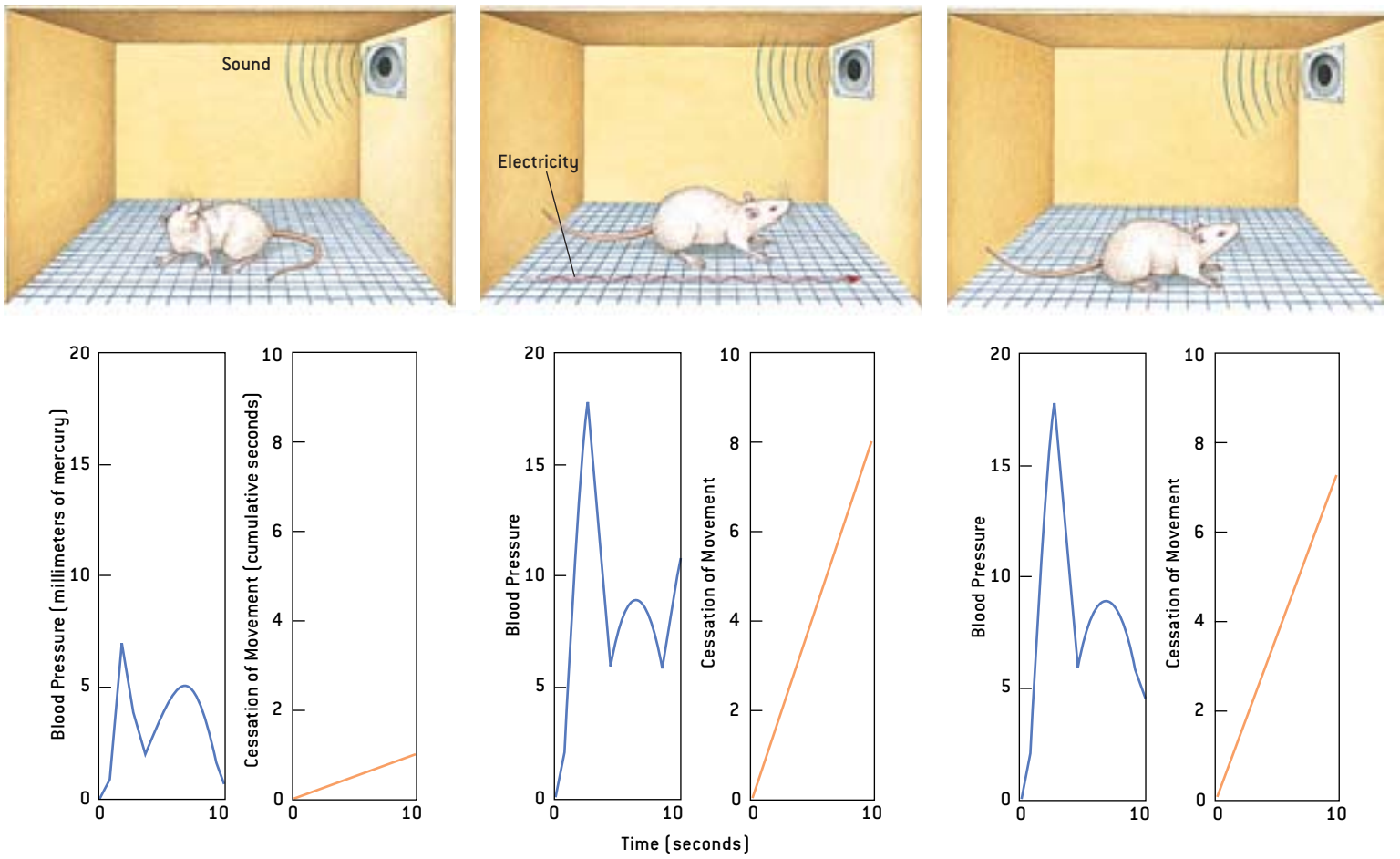

CLASSICAL FEAR CONDITIONING can be induced by pairing a sound and a mild electric shock to the foot of a rat. In one set of experiments, the rat hears a sound (*left*), which has little effect on the animal's blood pressure or patterns of movement. Next, the rat hears the same sound, coupled with a foot shock (*center*). After several such pairings, the rat's blood pressure rises at the same time that the animal freezes for an extended period when it hears the sound. The rat has been fear-conditioned (*right*): sound alone achieves the same physiological changes as did sound and shock together.

ing stimulus. We also demonstrated, in turn, that lesions in areas connected to the central nucleus eliminated one of the two responses. Michael Davis and his associates at Yale University determined that lesions of the central nucleus, as well as lesions of another brain stem area to which the central nucleus projects, diminished yet another conditioned response: the increased startle reaction that occurs when an animal is afraid.

The findings from various laboratories studying different species and measuring fear in different ways all implicated the central nucleus as a pivotal component of fear-conditioning circuitry. It provides connections to the various brain stem areas involved in the control of a spectrum of responses.

Despite our deeper understanding of this site in the amygdala, many details of the pathway remained hidden. Does sound, for example, reach the central nucleus directly from the auditory thalamus? We found that it does not. The central nucleus receives projections from thalamic areas next to, but not in, the auditory part of the thalamus; an entirely different area of the amygdala, the lateral nucleus, receives inputs from the auditory thalamus. Lesions of the lateral nucleus prevented fear conditioning.

Because this site gets information directly from the sensory system, we now consider it the sensory interface of the amygdala in fear conditioning. In contrast, the central nucleus appears to interface with the systems that control responses.

These findings seemed to place us on the threshold of being able to map the entire stimulus response pathway. But we still did not know how information received by the lateral nucleus arrived at the central nucleus. Earlier studies had suggested that the lateral nucleus projects directly to the central nucleus, but the connections were fairly sparse. Working with monkeys, David Amaral and Asla Pitkanen of the Salk Institute for Biological Studies in San Diego demonstrated that the lateral nucleus extends directly to an adjacent site, called the basal or basolateral nucleus, which, in turn, projects to the central nucleus.

Collaborating with Lisa Stefanacci and other members of the Salk team, Claudia R. Farb and C. Genevieve Go in my laboratory at New York University found the same connections in the rat. We then showed that these connections form synaptic contacts—communicating directly, neuron to neuron. Such contacts indicate that information reaching the lat-

ROBERTO OSTI (*top*); IAN WORPOLE (*bottom*)

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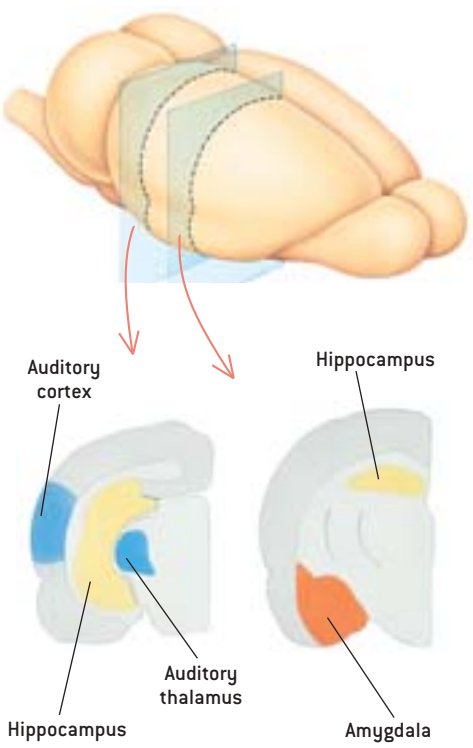

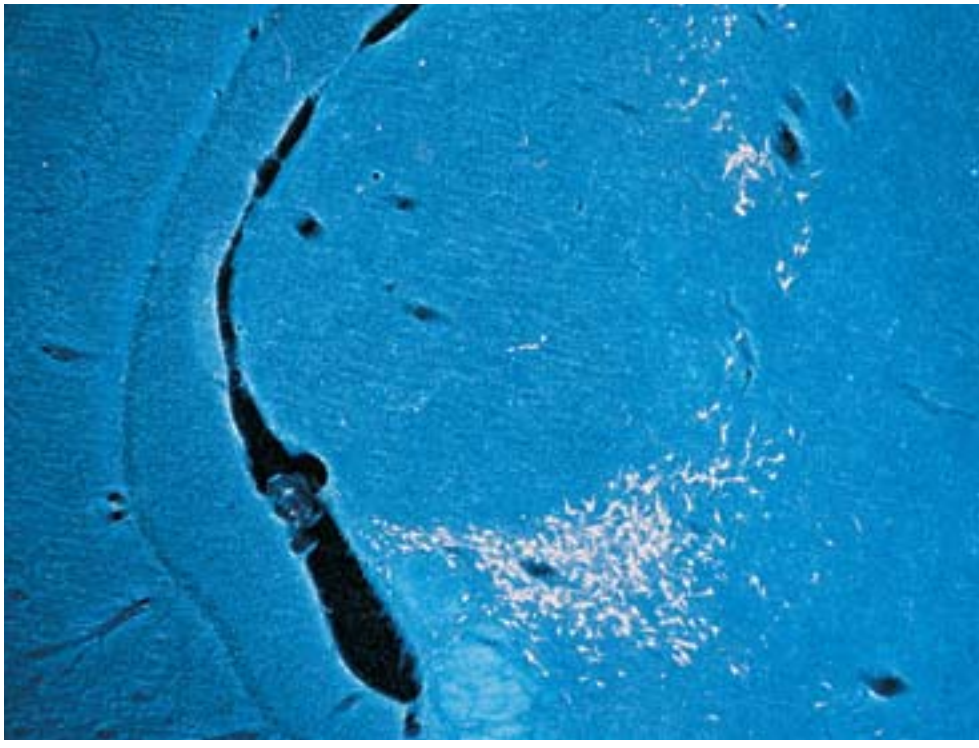

ANATOMY OF EMOTION includes several brain regions. Shown here in the rat, parts of the amygdala, the thalamus and the cortex interact to create memories about fearful experiences, associated here with sound. Work in the past decade has located where fear is learned and remembered: certain parts

eral nucleus can influence the central nucleus via the basolateral nucleus. The lateral nucleus can also influence the central nucleus by way of the accessory basal or basomedial nucleus. Clearly, ample opportunities exist for the lateral nucleus to communicate with the central nucleus once a stimulus has been received.

The emotional significance of such a stimulus is determined by the sound itself and by the environment in which it occurs. Rats must therefore learn not only that a sound or visual cue is dangerous but under what conditions it is so. Russell G. Phillips and I examined the response of rats to the chamber, or context, in which they had been conditioned. We found that lesions of the amygdala interfered with the animals' response to both the tone and the chamber. But lesions of the hippocampus—a brain region involved in declarative memor—interfered only with response to the chamber, not the tone. Declarative memory involves explicit, consciously accessible information, as well as spatial memory. At about the same time, Michael S. Fanselow and Jeansok J. Kim of the University of California at Los Angeles discovered that hippocampal lesions made after fear conditioning had taken place also prevented the expression of responses to the surroundings.

Emotional Significance

THESE FINDINGS were consistent with the generally accepted view that the hippocampus plays an important role in processing complex information, such as details about the spatial environment where activity is taking place. Phillips and I also demonstrated that the subiculum, a region of the hippocampus that projects to other areas of the brain, communicated with the lateral nucleus of the amygdala. This connection suggests that contextual information may acquire emotional significance in the same way that other events do—via transmission to the lateral nucleus.

Although our experiments had identified a subcortical sensory pathway that gave rise to fear conditioning, we did not dismiss the importance of the cortex. The interaction of subcortical and cortical mechanisms in emotion remains a hotly debated topic. Some researchers believe cognition is a vital precursor to emotional experience; others think that cognition—which is presumably a cortical function—is necessary to initiate emotion or that emotional processing is a type of cognitive processing. Still others question whether cognition is necessary for emotional processing.

It became apparent to us that the auditory cortex is involved in, though not crucial to, establishing the fear response, at least when simple auditory stimuli are applied. Norman M. Weinberger and his col-

THE AUTHOR

JOSEPH E. LeDOUX is the Henry and Lucy Moses Professor of Science at New York University. His research is focused on brain mechanisms of emotion and memory. He is the recipient of two National Institute of Mental Health distinctions: a Merit Award and a Research Scientist Development Award. LeDoux's 1996 book, *The Emotional Brain* (Simon & Schuster), was an elaboration of the basic ideas in this *Scientific American* article. His new book, *Synaptic Self* (Viking Penguin), presents a theory of how broad networks in the brain, especially those involved in emotion and memory, are key to understanding the neural basis of personality.

ROBERTO OSTI (*illustrations*); ANDREW LEONARD *APL Microscopic* (*photographs*)

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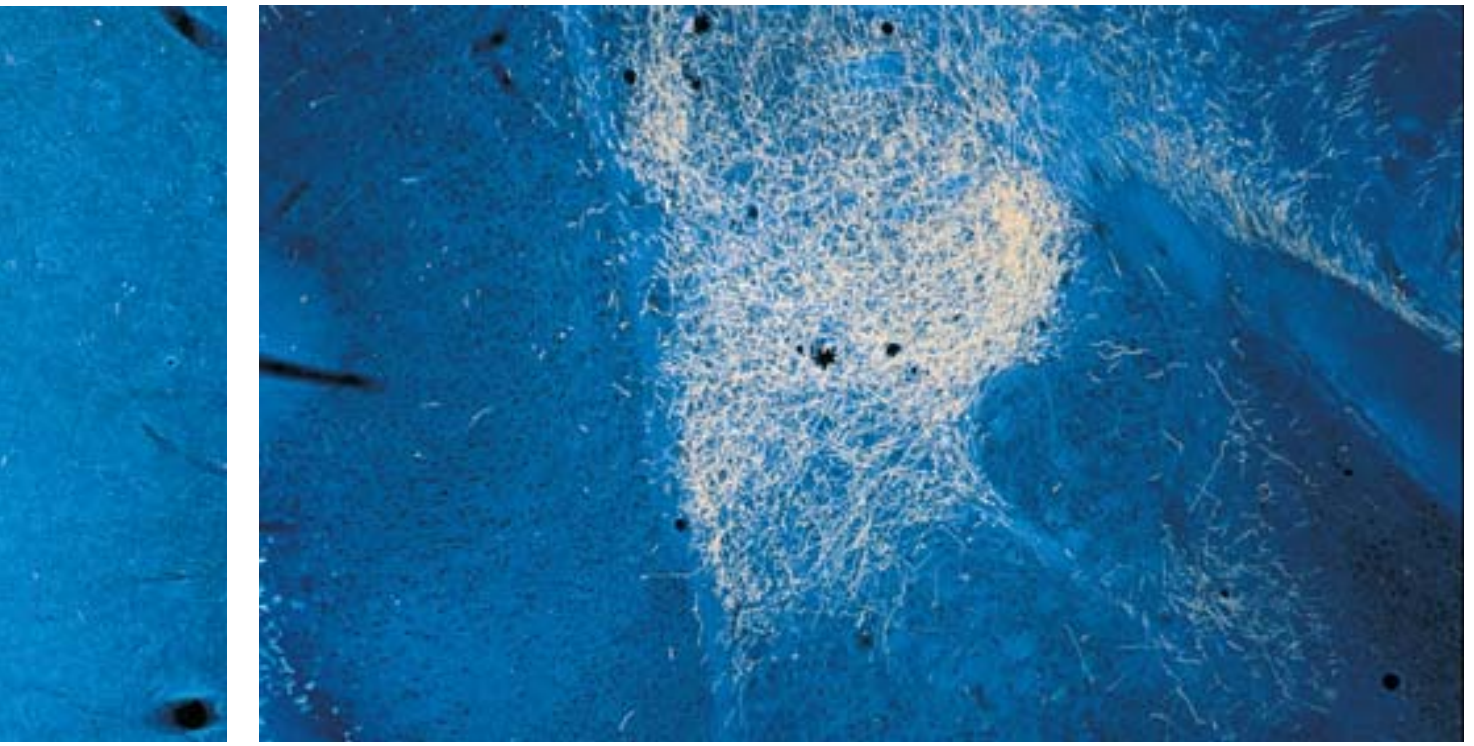

of the thalamus (*pink, left*) communicate with areas in the amygdala (*yellow, right*) that process the fear-causing sound stimuli. These neural mechanisms are thought to be similar in humans, so the study of emotional memory in rodents may illuminate aspects of human fear disorders.

leagues at the University of California at Irvine performed elegant studies showing that neurons in the auditory cortex undergo specific physiological changes in their reaction to sounds as a result of conditioning. This finding indicates that the cortex is establishing its own record of the event.

Experiments by Lizabeth M. Romanski in my laboratory determined that in the absence of the auditory cortex, rats can learn to respond fearfully to a single tone. If, however, projections from the thalamus to the amygdala are removed, projections from the thalamus to the cortex and then to the amygdala are sufficient. Romanski went on to establish that the lateral nucleus can receive input from both the thalamus and the cortex. Her work with rats complements earlier research in primates.

Molecular Mechanisms

ONCE WE HAD a clear understanding of the mechanism through which fear conditioning is learned, we tried to find out how emotional memories are established and stored on a molecular level. Farb and I showed that the excitatory amino acid transmitter glutamate is present in the thalamic cells that reach the lateral nucleus. Chiye J. Aoki and I showed that it is also present at synapses in the lateral nucleus. Because glutamate transmission is implicated in memory formation, we seemed to be on the right track.

Glutamate has been observed in a process called long-term potentiation, or LTP, that has emerged as a model for the creation of memories. This process, which is most frequently studied in the hippocampus, involves a change in the efficiency of synaptic transmission along a neural pathway—in other words, signals travel more readily along this pathway once LTP has taken place. The mechanism seems to involve glutamate transmission and a class of postsynaptic excitatory amino acid receptors known as NMDA (for *N*-methyl-D-aspartate) receptors.

Various studies have found LTP in the fear-conditioning pathway. Marie-Christine Clugnet and I noted that LTP could be induced in the thalamo-amygdala pathway. Thomas H. Brown and Paul Chapman and their colleagues at Yale discovered LTP in a cortical projection to the amygdala. Other researchers, including Davis and Fanselow, were able to block fear conditioning by blocking NMDA receptors in the amygdala. And Michael T. Rogan in my laboratory found that the processing of sounds by the thalamo-amygdala pathway is amplified after LTP has been induced. The fact that LTP can be demonstrated in a conditioning pathway offers new hope for understanding how LTP might relate to emotional memory.

Studies by Fabio Bordi, also in my laboratory, have suggested hypotheses about what is going on in the neurons of the lateral nucleus during learning. Bordi monitored the electrical state of individual neurons in this area when a rat was listening to the sound and receiving the shock. He and Romanski found that essentially every cell responding to the auditory stimuli also responded to the shock. The basic ingredient of conditioning is thus present in the lateral nucleus.

Bordi was able to divide the acoustically stimulated cells into two classes: habituating and consistently responsive.

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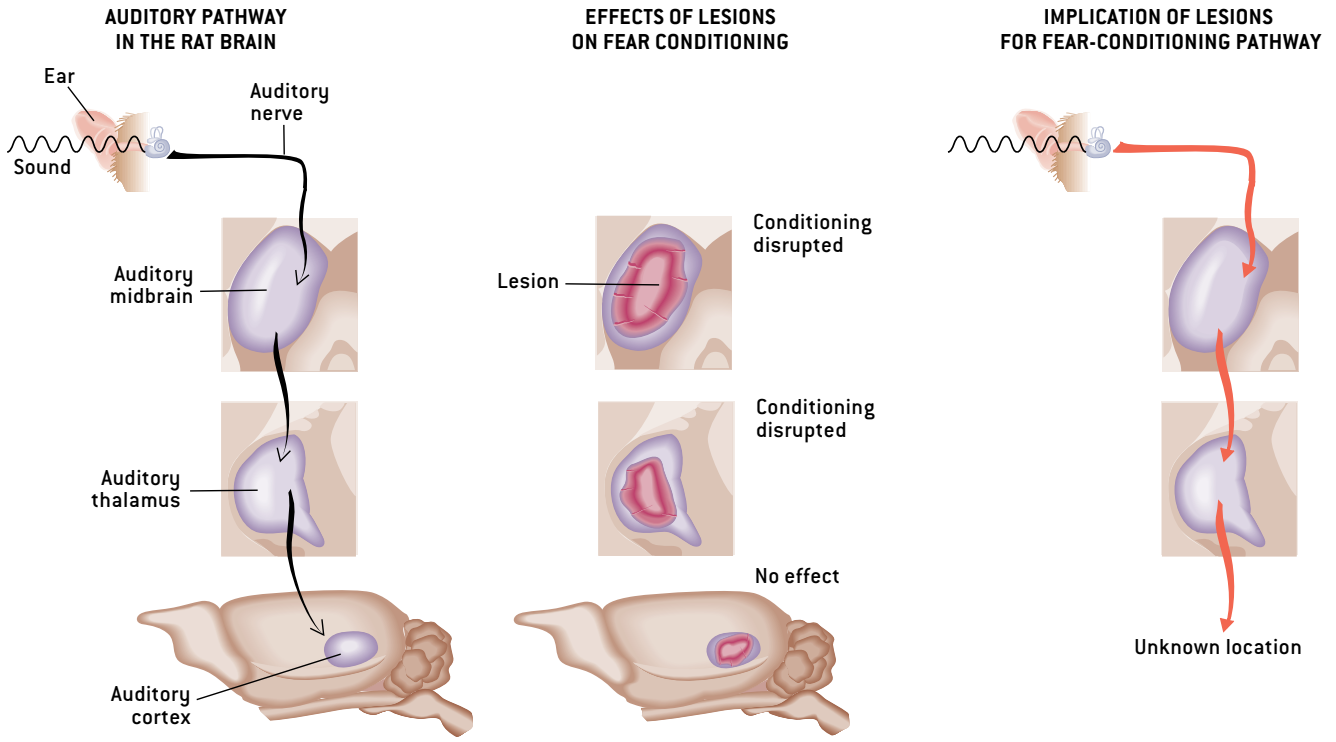
Habituating cells eventually stopped responding to the repeated sound, suggesting that they might serve to detect any sound that was unusual or different. They could permit the amygdala to ignore a stimulus once it became familiar. Sound and shock pairing at these cells might reduce habituation, thereby allowing the cells to respond to, rather than ignore, significant stimuli.

The consistently responsive cells had high-intensity thresholds: only loud sounds could activate them. That finding is interesting because of the role volume plays in judging distance. Nearby sounds are presumably more dangerous than those that are far away. Sound coupled with shock might act on these cells to lower their threshold, increasing the cells' sensitivity to the same stimulus. Consistently responsive cells were also broadly tuned. The joining of a sound and a shock could make the cells responsive to a narrower frequency range or could shift the tuning toward the frequency of the stimulus. Weinberger has shown that cells in the auditory system do alter their tuning to approximate the conditioned stimulus. Bordi and I detected this effect in lateral nucleus cells as well.

The apparent permanence of these memories raises an important clinical question: Can emotional learning be eliminated, and, if not, how can it be toned down? It appears to be quite difficult to get rid of emotional memories, and at best we can hope only to keep them under wraps. Studies by Maria A. Morgan in my laboratory have illuminated how the brain regulates emotional expressions. Morgan showed that when part of the prefrontal cortex is damaged, emotional memory is very hard to extinguish. This discovery indicates that the prefrontal areas—possibly by way of the amygdala—normally control expression of emotional memory and prevent emotional responses once they are no longer useful. A similar conclusion was proposed by Edmund T. Rolls and his colleagues at the University of Oxford during primate studies. The researchers studied the electrical activity of neurons in the frontal cortex of the animals.

The apparent permanence of these memories raises an important CLINICAL QUESTION: Can emotional memory be eliminated?



BRAIN LESIONS have been crucial to pinpointing the sites involved in experiencing and learning about fear. When a sound is processed by the rat brain, it follows a pathway from ear to midbrain to thalamus to cortex (*left*). Lesions can be made in various sites in the auditory pathway to determine which areas are necessary for fear conditioning (*center*). Only damage to the cortex does not disrupt the fear response, which suggests that some other areas of the brain receive the output of the thalamus and are involved in establishing memories about experiences that stimulate fear (*right*).

IAN WORPOLE

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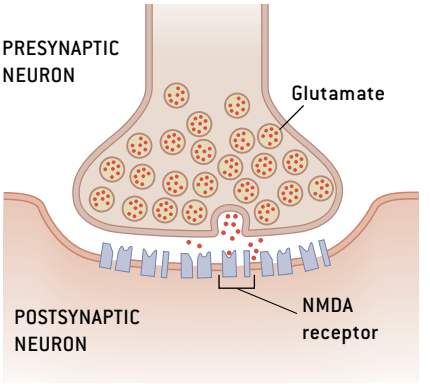
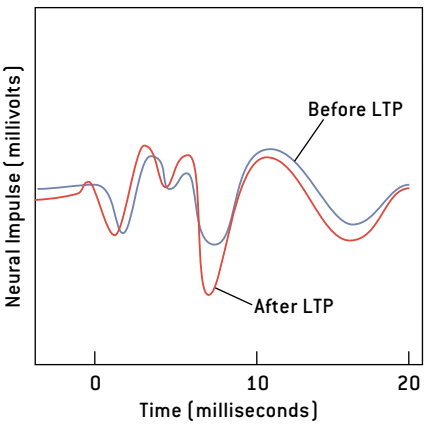
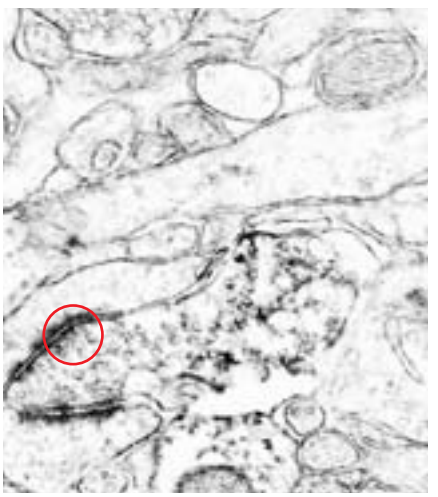
CREATION OF MEMORY has been linked to a process called long-term potentiation, or LTP, in which the neurotransmitter glutamate and its NMDA (for *N*-methyl-D-aspartate) receptors bring about strengthened neural transmission. Once LTP is established, the same neural signals produce larger responses (*right*). Emotional memories may also involve LTP in the amygdala. Glutamate (*red circle in top micrograph*) and NMDA receptors (*red circle in bottom micrograph*) have been found in the region of the amygdala where fear conditioning takes place.







Functional variation in the pathway between this region of the cortex and the amygdala may make it more difficult for some people to change their emotional behavior. Davis and his colleagues found that blocking NMDA receptors in the amygdala interferes with extinction, which hints that it is an active learning process. Such learning could be situated in connections between the prefrontal cortex and the amygdala. More experiments should disclose the answer.

Placing a basic emotional memory process in the amygdalic pathway yields obvious benefits. The amygdala is a critical site of learning because of its central location between input and output stations. Each route that leads to the amygdala—sensory thalamus, sensory cortex and hippocampus—delivers unique information. Pathways originating in the sensory thalamus provide only a crude perception of the external world, but because they involve only one neural link, they are quite fast. In contrast, pathways from the cortex offer detailed and accurate representations, allowing us to recognize an object by sight or sound. But these pathways, which run from the thalamus to the sensory cortex to the amygdala, involve several neural links. And each link in the chain adds time.

Conserving time may be the reason there are two routes—one cortical and one subcortical—for emotional learning. Animals, and humans, need a quick-and-dirty reaction mechanism. The thalamus activates the amygdala at about the same time as it activates the cortex. The arrangement may enable emotional responses to begin in the amygdala before we completely recognize what it is we are reacting to or what we are feeling.

The thalamic pathway may be particularly useful in situations requiring a rapid response. Failing to respond to danger is more costly than responding inappropriately to a benign stimulus. For instance, the sound of rustling leaves is enough to alert us when we are walking in the woods without our first having to identify what is causing the sound. Similarly, the sight of a slender curved shape lying flat on the path ahead of us is sufficient to elicit defensive fear responses [*see illustration on page 63*]. We do not need to go through a detailed analysis of whether or not what we are seeing is a snake. Nor do we need to identify the snake as a reptile or note that its skin can be used to make belts and boots. All these details are irrelevant and, in fact, detrimental to an efficient, speedy and potentially lifesaving reaction. The brain simply needs to be able to store primitive cues and detect them. Later, coordination of this basic information with the cortex permits verification (yes, this is a snake) or brings the response (screaming, sprinting) to a stop.

Storing Emotional Memory

ALTHOUGH THE AMYGDALA stores primitive information, we should not consider it the only learning center. The establishment of memories is a function of the entire network, not just of one component. The amygdala is certainly crucial, but we must not lose sight of the fact that its functions exist only by virtue of the system to which it belongs.

Memory is generally thought to be the process by which we bring back to mind some earlier conscious experience. The original learning and the remembering, in this case, are both conscious events. Researchers have determined that declarative memory is mediated by the hippocampus and the cortex. But removal of the hippocampus has little effect on fear conditioning—except conditioning to context.

In contrast, emotional learning that comes through fear conditioning is not declarative learning. Rather it is mediated by a different system, which may operate independently of conscious awareness. Emotional information may be

IAN WORPOLE (*illustrations*); JOSEPH E. LEDOUX (*micrographs*)

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stored within declarative memory, but it is kept there as a cold declarative fact. For example, if a person is injured in an auto accident in which the horn gets stuck, he or she may later react when hearing the blare of car horns. The person may remember the details of the accident, such as where and when it occurred and who was involved. These are declarative memories that are dependent on the hippocampus. The individual may also become tense, anxious and depressed as the emotional memory is reactivated through the amygdalic system. The declarative system has stored the emotional content of the experience, but it has done so as a fact.

Emotional and declarative memories are stored and retrieved in parallel, and their activities are joined seamlessly in our conscious experience. That does not mean that we have direct conscious access to our emotional memory; it means instead that we have access to the consequences—such as the way we behave or the way our bodies feel. These consequences combine with current declarative memory to form a new declarative memory. Emotion is not just unconscious memory: it exerts a powerful influence on declarative memory and other thought processes. As James L. McGaugh and his colleagues at the University of California at Irvine have convincingly shown, the amygdala plays an essential part in modulating the storage and strength of memories.

The distinction between declarative memory and emotional memory is an important one. W. J. Jacobs of the University of British Columbia and Lynn Nadel of the University of Arizona have argued that we are unable to remember traumatic early-life events because the hippocampus has not yet matured enough to consciously form accessible memories. The emotional memory system, which may develop earlier, clearly forms and stores its unconscious memories of these events. For this reason, the trauma may affect mental and behavioral functions in later life through processes that remain inaccessible to consciousness.

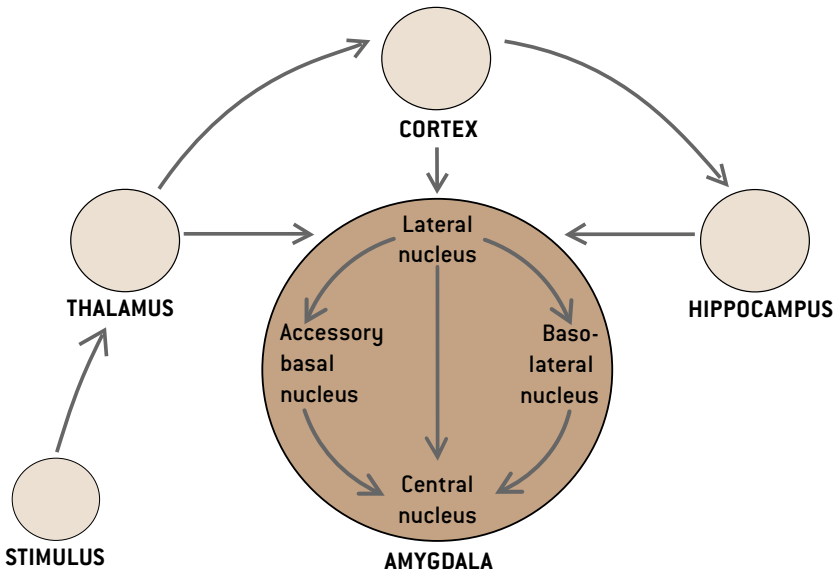
Because pairing a tone and a shock can bring about conditioned responses in animals throughout the phyla, it is clear that fear conditioning cannot be dependent on consciousness. Fruit flies and snails, for example, are not creatures known for their conscious mental processes. My way of interpreting this phenomenon is to consider fear a subjective state of awareness brought about when brain systems react to danger. Only if the organism possesses a sufficiently advanced neural mechanism does conscious fear accompany bodily response. This is not to say that only humans experience fear but, rather, that consciousness is a prerequisite to subjective emotional states.

Thus, emotions or feelings are conscious products of unconscious processes. It is crucial to remember that the subjective experiences we call feelings are not the primary business of the system that generates them. Emotional experiences are the result of triggering systems of behavioral adaptation that have been preserved by evolution. Subjective experience of any variety is challenging turf for scientists. We have, however, gained understanding about the neural system that underlies fear responses. This same system may give rise to subjective feelings of fear.

> Emotion is not just unconscious memory: it exerts a POWERFUL INFLUENCE on declarative memory and other THOUGHT PROCESSES.

Structure of the Amygdala

THE AMYGDALA plays an important role in emotional behavior. Experiments in rodents have elucidated the structures of various regions of the amygdala and their role in learning about and remembering fear. The lateral nucleus receives inputs from sensory regions of the brain and transmits these signals to the basal, the accessory basal and the central nuclei. The central nucleus connects to the brain stem, bringing about physiological changes. —*J.E.LeD.*



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If so, studies of the neural control of emotional responses may also hold the key to understanding subjective emotion.

Postscript

MUCH HAS HAPPENED in the study of emotion, memory and the brain since this article was written in 1994, some of which I will summarize.

Additional studies have extended our understanding of the anatomical organization of the amygdala. This work affirms the importance of the lateral nucleus as the gateway into the amygdala and further suggests that information processing occurs at the level of subregions with the lateral nucleus. The importance of the subregional organization of the lateral amygdala is also emphasized by studies in which the activity of neurons has been recorded in response to a tone conditioned stimulus (CS) before and after fear conditioning. The results showed that the CS-elicited activity in the dorsal subnucleus of the lateral amygdala increases dramatically through pairing of the CS with the foot-shock unconditioned stimulus and that different populations of cells in this area are involved in initial learning and in memory storage. Because the cellular activity is learned before fear is expressed, the cellular changes are a plausible part of the explanation of how fear behavior is learned and remembered.

The molecular mechanisms underlying fear learning and memory have been pursued through studies of LTP in brain slices of the lateral amygdala. This work suggests that the induction of LTP can take place by either of two mechanisms. Both of these mechanisms require the influx of calcium into lateral amygdala cells that are postsynaptic—that is, on the receiving end of the signal—to the sensory input pathways. One form of LTP involves calcium entry through voltage-gated calcium channels; the other involves NMDA receptors. Both of these are cellular pathways that, when opened, allow calcium ions to enter the cell. Other studies showed that in live animals, fear conditioning, like LTP, depends on NMDA receptors and the voltage-gated calcium channels. Also, fear conditioning alters neural activity in the lateral amygdala in a manner that closely resembles what happens when LTP is induced in this region, suggesting that LTP is a plausible model of learning.

The elevation of calcium that occurs in postsynaptic neurons during LTP and fear learning triggers a cascade of other chemical processes that leads to a sustained state of enhanced synaptic efficacy between the pre- and postsynaptic neurons. This is a cellular definition of memory. For fear conditioning and many other forms of learning in various species, elevated calcium activates catalytic enzymes called protein kinases (MAP kinase and protein kinase A, among others). These kinases then travel to the cell nucleus, where they activate gene transcription factors (such as CREB), which initiate the synthesis of RNA and proteins. The proteins then travel back to the previously active synapses and stabilize the connection. Because similar molecular steps are involved in different forms of memory in different species, it seems that the uniqueness of different kinds of memory has less to do with the underlying molecules than with the circuits in which they act.

Protein synthesis is not only involved in the initial formation of the memory of an aversive experience but is also called into play when these memories are recalled, which suggests that each time such a memory is activated it has to be restored (reconsolidated) by new protein synthesis. This may be a process by which memories are updated in light of experiences that occurred after the initial memory.

Stimulated by progress in rodent studies, researchers have begun to examine fear processing in the human brain.

MEMORIES of disturbing experiences form deep within our brains.

Studies of patients with damage to the amygdala have shown that this region is required for fear conditioning and other aspects of emotional memory. And functional imaging has shown that the human amygdala is activated during fear conditioning, even under conditions where the CS is prevented from entering consciousness, showing that fear memories can be established unconsciously.

Emotions and memory contribute significantly to our personality, our self. With so much progress made in understanding the brain mechanisms of emotion and memory, we can hope that new research will turn more toward questions about how these factors interact in the shaping of personality, an important topic that neuroscientists have not considered in much detail so far. SA

MORE TO EXPLORE

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the neurobiology of FEAR

RESEARCHERS ARE TEASING APART THE PROCESSES IN THE BRAIN THAT GIVE RISE TO VARIOUS FEARS IN MONKEYS. THE RESULTS MAY LEAD TO NEW WAYS TO TREAT ANXIETY IN HUMANS

BY NED H. KALIN

OVER THE YEARS, most people acquire a repertoire of skills for coping with a range of frightening situations. They will attempt to placate a vexed teacher or boss and will shout and run when chased by a mugger. But some individuals become overwhelmed in circumstances others would consider only minimally stressful: fear of ridicule might cause them to shake uncontrollably when called on to speak in a group, or terror of strangers might lead them to hide at home, unable to work or shop for groceries. Why do certain people fall prey to excessive fear?

At the University of Wisconsin–Madison, my colleague Steven E. Shelton and I are addressing this problem by identifying specific brain processes that regulate fear and its associated behaviors. Despite the availability of noninvasive imaging techniques, such information is still extremely difficult to obtain in humans. Hence, we have turned our attention to another primate, the rhesus monkey (*Macaca mulatta*). These animals undergo many of the same physiological and psychological developmental stages that humans do, but in a more compressed time span. As we gain more insight into the nature and operation of neural circuits that modulate fear in monkeys, it should be possible to pinpoint the brain processes that cause inordinate anxiety in people and to devise new therapies to counteract it.

Effective interventions would be particularly beneficial if they were applied at an early age. Growing evidence suggests overly fearful youngsters are at high risk for later emotional distress. Jerome Kagan and his colleagues at Harvard University have shown, for example, that a child who is profoundly shy at the age of two years is more likely than a less inhibited child to suffer from anxiety and depression later in life.

This is not to say these ailments are inevitable. But it is easy to see how excessive fear could contribute to a lifetime of emotional struggle. Consider a child who is deeply afraid of other children and is therefore taunted by them at school. That youngster might begin to feel unlikable and, in turn, to withdraw further. With time the growing child could become mired in a vicious circle leading to isolation, low self-esteem, underachievement, and the anxiety and depression noted by Kagan.

There are indications that unusually fearful children might also be prone to

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Updated from the May 1993 issue

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physical illness. Many youngsters who become severely inhibited in unfamiliar situations chronically overproduce stress hormones, including the adrenal product cortisol. In times of threat, these hormones are critical. They ensure that muscles have the energy needed for "fight or flight." But some evidence indicates long-term elevations of stress hormones may contribute to gastric ulcers and cardiovascular disease.

Further, through unknown mechanisms, fearful children and their families are more likely than others to suffer from allergic disorders. And in rodents and nonhuman primates, persistent elevation of cortisol has been shown to increase the vulnerability of neurons in the hippocampus to damage by other substances; this brain region is involved in memory, motivation and emotion. Human neurons probably are affected in a similar way, although direct evidence is awaited.

When we began our studies two decades ago, Shelton and I knew we would first have to find cues that elicit fear and identify behaviors that reflect different types of anxiety. With such information in hand, we could proceed to determine the age at which monkeys begin to match defensive behaviors selectively to specific cues. By also determining the parts of the brain that reach maturity during the same time span, we could gain clues to the regions that underlie the regulation of fear and fear-related behavior.

The experiments were carried out at the Wisconsin Regional Primate Research Center and the Harlow Primate Laboratory, both at the University of Wisconsin–Madison. We discerned varied behaviors by exposing monkeys between six and 12 months old to three related situations. In the alone condition, an animal was separated from its mother and left by itself in a cage for 10 minutes. In the no-eye-contact condition, a person stood motionless outside the cage and avoided

RHESUS MONKEY REGISTERS ALARM (*right*) as another monkey approaches her baby. The mother's fear is evident in her "threat" face: the open mouth and piercing stare serve to intimidate would-be attackers and intruders.

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looking at the solitary infant. In the stare condition, a person was again present and motionless but, assuming a neutral expression, peered directly at the animal. These conditions are no more frightening than those that primates encounter frequently in the wild or those that human infants encounter every time they are left at a day-care center.

Three Typical Fear Behaviors

IN THE ALONE CONDITION, most monkeys became very active and emitted frequent "coo" calls. These fairly melodious sounds are made with pursed lips. They start at a low pitch, rise higher and then fall. More than 40 years ago Harry F. Harlow, then at Wisconsin, deduced that when an infant monkey is separated from its mother, its primary goal is affiliative—it yearns to regain the closeness and security provided by nearness to the parent. Moving about and cooing help to draw the mother's attention.

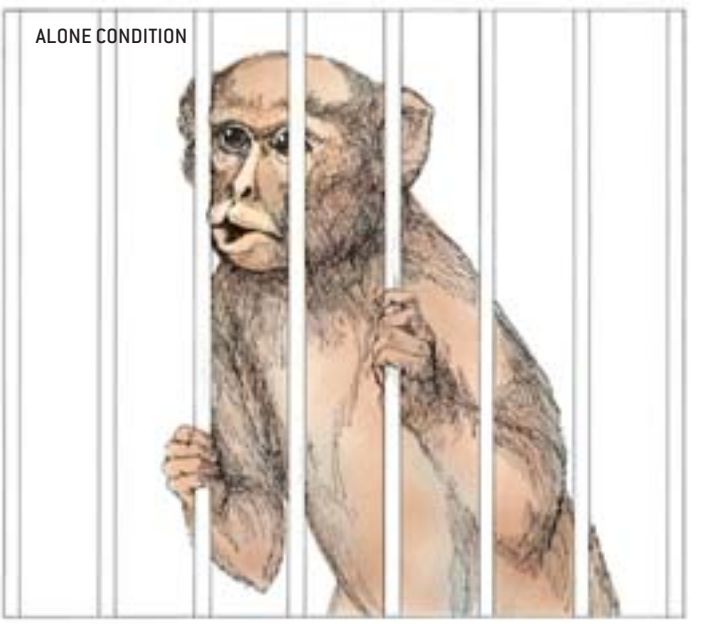
In contrast, in the more frightening no-eye-contact situation, the monkeys reduced their activity greatly and sometimes "froze," remaining completely still for prolonged periods. When an infant spots a possible predator, its goal shifts from attracting the mother to becoming inconspicuous. Inhibiting motion and freezing—common responses in many species—reduce the likelihood of attack.

If the infant perceives that it has been detected, its aim shifts to warding off an attack. So the stare condition evoked a third set of responses. The monkeys made several hostile gestures: "barking" (forcing air from the abdomen through the vocal cords to emit a growl-like sound), staring back, producing so-called threat faces, baring their teeth and shaking the cage. Sometimes the animals mixed the threatening displays with submissive ones, such as fear grimaces, which look something like wary grins, or grinding of the teeth. In this condition, the animals cooed more than they did when alone. (We have come to think the cooing displayed in the stare condition may serve a somewhat different function than it does in the alone situation.)

Monkeys, by the way, are not unique in becoming aroused by stares and in using them reciprocally to intimidate predators. Animals as diverse as crabs, lizards and birds all perceive staring as a threat. Some fishes and insects have evolved protective spots that resemble eyes; these spots either avert attacks completely or redirect them to nonvital parts of the body. In India, field-workers wear face masks behind their heads to discourage tigers from pouncing at their backs. Studies of humans show that we, too, are sensitive to direct gazes: brain activity increases when we are stared at, and people who are anxious or depressed tend to avoid direct eye contact.

Having identified three constellations of defensive behaviors, we set about determining when infant monkeys first begin to apply them effectively. Several lines of work led us to surmise that the ability to make such choices emerges sometime around an infant's two-month birthday. For instance, rhesus mothers generally permit children to venture off with their peers at that time, presumably because the adults are now confident that the infants can protect themselves reasonably well. We also knew that by about 10 weeks of age infant monkeys respond with different emotions to specific expressions on other monkeys' faces—a sign that at least some of the innate wiring or learned skills needed to discriminate threatening cues are in place.

To establish the critical period of development, we examined four groups of monkeys ranging in age from a few days to 12 weeks old. We separated the babies from their mothers and let them acclimate to an unfamiliar cage. Then we exposed



THREE experimental conditions elicit distinct fear-related behaviors in rhesus monkeys older than about two months. When isolated in a cage (*left*), youngsters become quite active and emit "coo" sounds to attract their mothers. If a human appears but avoids eye contact (*center*), the monkeys try to evade discovery, such as by staying completely still (freezing) or hiding behind their food bin. If the intruder stares at the animals (*right*), they become aggressive.

TYPICAL BEHAVIORS induced by the alone, no-eye-contact and stare conditions in the laboratory—such as cooing (*left*), freezing (*center*) and hostile display of the teeth (*right*)—are also seen in frightened infants and adults living in the wild. In this case, the setting is Cayo Santiago, an island off the mainland of Puerto Rico.

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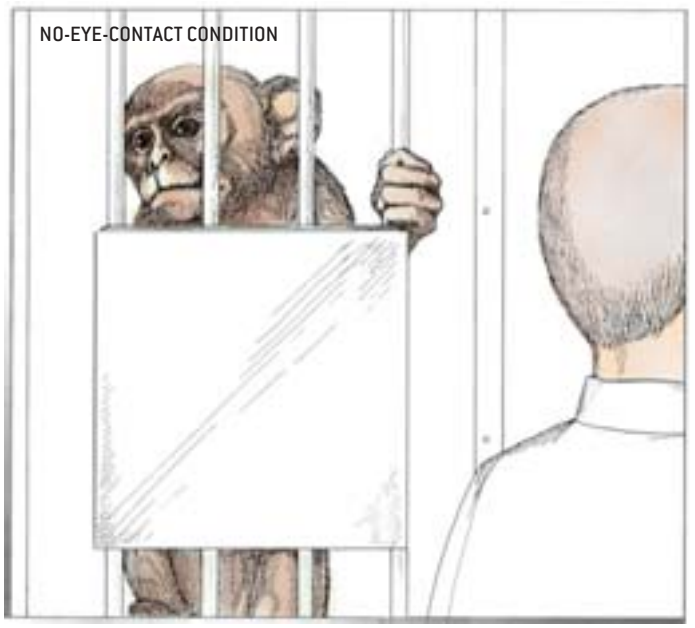

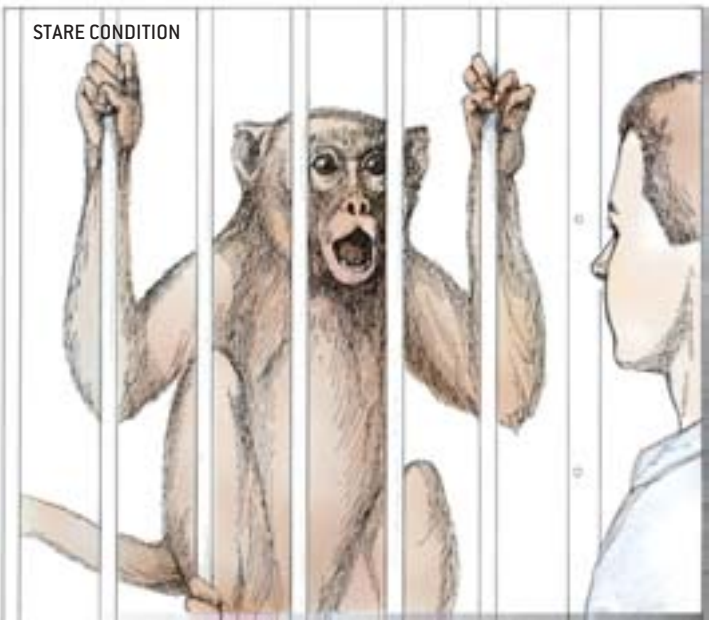

them to the alone, no-eye-contact and stare conditions. All sessions were videotaped for analysis.

We found that infants in the youngest group (newborns to two-week-olds) engaged in defensive behaviors. But they lacked some motor coordination and seemed to act randomly, as if they were oblivious to the presence or gaze of the human intruder. Babies in our two intermediate-age groups had good motor control, but their actions seemed unrelated to the test condition. This finding meant motor control was not the prime determinant of selective responding.

Only animals in our oldest group (nine- to 12-week-olds) conducted themselves differently in each situation, and their reactions were both appropriate and identical to those of mature monkeys. Nine to 12 weeks, then, is the critical age for the appearance of a monkey's ability to adaptively modulate its defensive activity to meet changing demands.

Studies by other workers, primarily with rodents, suggested that three interconnected parts of the brain regulate fearfulness. We suspected that these regions become functionally mature during the nine- to 12-week period and thus give rise to the selective reactivity we observed. One of these regions is the prefrontal cortex, which takes up much of the outer and side areas of the cerebral cortex in the frontal lobe [*see illustration on next page*]. A cognitive and emotional area, the prefrontal cortex is thought to participate in the interpretation of sensory stimuli and is probably a site where

NED H. KALIN (*photographs*); CAROL DONNER (*illustrations*)

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the potential for danger is assessed.

The second region is the amygdala, a part of a primitive area in the brain called the limbic system (which includes the hippocampus). The limbic system in general and the amygdala in particular have been implicated in generating fear. instance, during this time the formation of synapses (contact points between neurons) has been shown to reach its peak in the prefrontal cortex and the limbic system (including the amygdala), as well as in the motor and visual cortices and other sensory areas. Patricia S. Goldman-Rakic of Yale University has also established that as the prefrontal cortex matures in rhesus monkeys, the ability to guide behavior based on experience emerges. This skill is necessary if one is to contend successfully with danger.

Maturation of the prefrontal cortex likewise seems important for enabling humans to distinguish among threatening cues. Harry T. Chugani, then at the University of California at Los Angeles, and his co-workers have shown that activity in the prefrontal cortex increases when human offspring are seven to 12 months of age. During this span—which appears to be analogous to the time when monkeys begin to respond selectively to fear—children begin to display marked fear of strangers. They also become adept at what is called social referencing; they regulate their level of fear based on the expressions they observe on a parent's face.

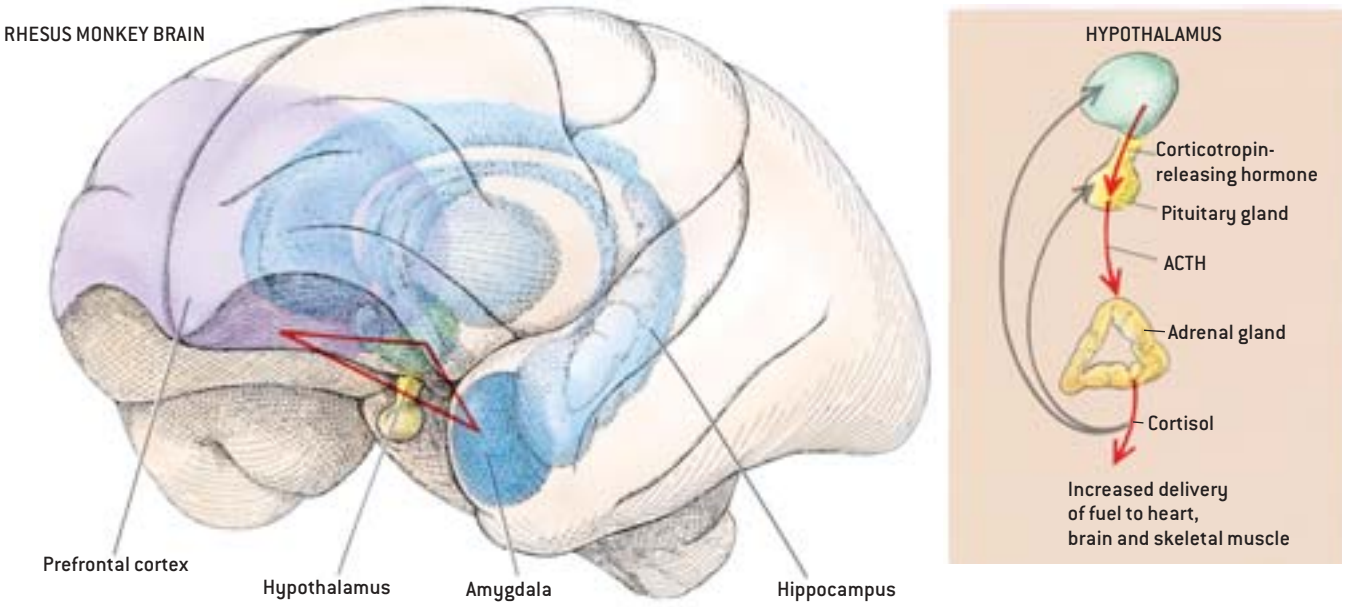
But what of the hypothalamus, the third brain region we assumed could participate in regulating fear-related behavior? Published research did not tell us much about its development or about the development of the complete hypothalamic-pituitary-adrenal system in monkeys. Our own investigations, however, revealed that the full system matures in parallel with that of the prefrontal cortex and the limbic system.

Levels of stress hormones influence how appropriately animals and people behave in the face of fear.

The final region is the hypothalamus. Located at the base of the brain, it is part of the hypothalamic-pituitary-adrenal system. In response to stress signals from elsewhere in the brain, such as the limbic system and other cortical regions, the hypothalamus secretes corticotropin-releasing hormone. This small protein spurs the pituitary gland, located just below the brain, to secrete adrenocorticotropic hormone (ACTH), which prods the adrenal gland to release cortisol, which prepares the body to defend itself.

In neuroanatomic data collected in other laboratories, we found support for our suspicion that maturation of these brain regions underlies selective responding in the nine- to 12-week period. For

In these studies, we used the pituitary hormone ACTH as a marker of the system's function. We again examined four groups of rhesus infants from a few days old to 12 weeks old. From each subject, we measured ACTH levels in blood drawn while the baby was with its mother. This reading provided a baseline. We also measured ACTH levels in blood samples obtained 20 minutes after the infant



THREE BRAIN REGIONS that are interconnected by neural pathways (*shown schematically by red lines*) are critically important in regulating fear-related behaviors. The prefrontal cortex (*purple*) participates in assessing danger. The amygdala (*dark blue*) is a major constituent of the emotion-producing limbic system (*light blue*). And the hypothalamus (*green*), in response to signals from the prefrontal cortex, amygdala and hippocampus, directs the release of hormones (*red arrows in box*) that support motor responses to perceived threats. (*Gray arrows represent inhibitory activity by cortisol.*)

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was separated from its parent. Hormonal levels rose in all four age groups during separation, but they jumped profoundly in the oldest (nine- to 12-week-old) monkeys.

The relatively weak response in the younger animals, particularly in those under two weeks old, is consistent with findings in rat pups, whose stress hormone response is also blunted during the first two weeks of life. The development of the rodent and primate stress hormone system may well be delayed during early life to protect young neurons from the potentially damaging effects of cortisol.

Assured that the hypothalamic-pituitary-adrenal system becomes functionally mature by nine to 12 weeks, we pressed the inquiry forward to determine whether levels of cortisol and ACTH might partly account for individual differences in defensive behavior. We were also curious to know whether the responses of the infants resembled those of their mothers; a correspondence would indicate that further analyses of mothers and their infants could help reveal the relative contributions of inheritance and learning to fearfulness. We mainly examined the propensity for freezing, which we had earlier found was a stable trait in our subjects.

Maturing Fear Response

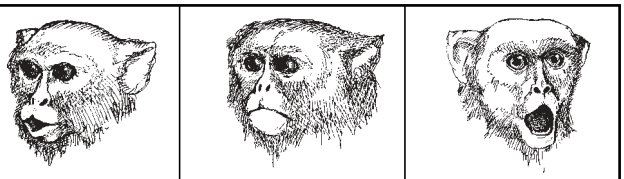
IN ONE SET OF STUDIES, we measured baseline levels of cortisol in monkeys four months to a year old and then observed how much time the youngsters froze in the no-eye-contact condition. Monkeys that started off with relatively low levels of cortisol froze for shorter periods than did their counterparts with higher cortisol levels—a pattern we also noted in separate studies of adult females. In other studies, we observed that as youngsters pass through their first year of life, they become progressively like their mothers hormonally and behaviorally. By the time infants are about five months old, their stress-induced rises in ACTH levels parallel those of their mothers. And by the time they are a year old, the duration of freezing in the no-eye-contact condition also corresponds to that of the mother.

Strikingly, some of these results echoed those obtained in humans. Extremely inhibited children often have parents who suffer from anxiety. Moreover, Kagan and his colleagues have found that basal cortisol levels are predictive of such children's reaction to a frightening situation. They measured cortisol concentrations in saliva of youngsters at home (where they are presumably most relaxed) and then observed the children confronting an unfamiliar situation in the laboratory; high basal cortisol levels were associated with greater inhibition in the strange setting.

These similarities between humans and monkeys again imply that monkeys are reasonable models of human emotional reactivity. The link between basal cortisol levels and duration of freezing or inhibition suggests as well that levels of stress hormones influence how appropriately animals and people behave in the face of fear. (This effect may partly be mediated by the hippocampus, where the concentration of cortisol receptors is high.) And the likeness of hormonal and behavioral responses in mothers and infants implies that genetic inheritance might predispose some individuals to extreme fearfulness, although we cannot rule out the contribution of experience.

No one can yet say to what extent the activity of the hypothalamic-pituitary-adrenal system controls, and is controlled by, other brain regions that regulate the choice of defensive behavior. We have, however, begun to identify distinct neurochemical circuits, or systems, in the brain that affect different behaviors. The two systems we have studied most intensely seemed at first to have quite separate functions. But more recent work implies that the controls on defensive behavior are rather more complicated than the original analyses implied.

We gathered our initial data more than a decade ago by treating six- to 12-month-old monkeys with two different classes of neuroactive chemicals—opiates (morphinelike substances) and benzodiazepines (chemicals that include the antianxiety drug diazepam, or Valium). We chose to look at opiates and benzodiazepines because neurons that release or take



	COOING	FREEZING	BARKING
MORPHINE (OPIATE)	Decreases	No effect	No effect
NALOXONE (OPIATE BLOCKER)	Increases	No effect	No effect
DIAZEPAM (BENZODIAZEPINE)	No effect	Decreases	Decreases

EFFECTS ON COOING, FREEZING AND BARKING were evaluated some years ago for three drugs that act on neurons responsive to opiates (*top two rows*) or to benzodiazepines (*bottom row*). The results implied that opiate-sensitive pathways in the brain control affiliative behaviors (those that restore closeness to the mother, as cooing often does), whereas benzodiazepine-sensitive pathways control responses to immediate threats (such as freezing and barking). Newer evidence generally supports this conclusion but adds some complexity to the picture.

THE AUTHOR

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up those chemicals are abundant in the prefrontal cortex, the amygdala and the hypothalamus. The opiates are known to have natural, or endogenous, counterparts, called endorphins and enkephalins, that serve as neurotransmitters; after the endogenous chemicals are released by certain neurons, they bind to receptor molecules on other nerve cells and thereby increase or decrease nerve cell activity. Receptors for benzodiazepines have been identified, and investigators are attempting to characterize endogenous benzodiazepinelike molecules.

Selective Drug Effects

ONCE AGAIN, our subjects were exposed to the alone, no-eye-contact and stare conditions. We delivered the drugs before the infants were separated from their mothers and then recorded the animals' behavior. Morphine decreased the amount of cooing normally displayed in the alone and stare conditions. Conversely, cooing was increased by naloxone, a compound that binds to opiate receptors but blocks the activity of morphine and endogenous opiates. Yet morphine and naloxone had no influence on the frequency of stare-induced barking and other hostile behaviors, nor did they influence duration of freezing in the no-eye-contact situation. We concluded that opiate-using neural pathways primarily regulate affiliative behaviors (such as those induced by distress over separation from the mother), but those pathways seem to have little power over responses to direct threats.

The benzodiazepine we studied—diazepam—produced a contrary picture. The drug had no impact on cooing, but it markedly reduced freezing, barking and other hostile gestures. Thus, benzodiazepine-using pathways seemed primarily to influence responses to direct threats but to have little power over affiliative behavior.

We still think the opiate and benzodiazepine pathways basically serve these separate functions. But the simple model we initially envisioned grew more interesting as we investigated two additional drugs: a benzodiazepine called alprazolam (Xanax) and a compound called beta-carboline, which binds to benzodiazepine receptors but elevates anxiety and typically produces effects opposite to those of diazepam and its relatives. When we administered alprazolam in doses that lower anxiety enough to decrease freezing, this substance, like diazepam, minimized hostility in the threatening, stare condition. And beta-carboline enhanced hostility. No surprises here. Yet, unlike diazepam, these drugs modulated cooing, which we had considered to be an affiliative (opiate-controlled) behavior, not a threat-related (benzodiazepine-controlled) one. Moreover, both these compounds decreased cooing. We cannot explain the similarity of effect, but we have some ideas about why drugs that act on benzodiazepine receptors might influence cooing.

It may be that, contrary to our early view, benzodiazepine pathways can in fact regulate affiliative behavior. We favor a second interpretation, however. Cooing displayed in the stare condition may not solely reflect an affiliative need (a desire for mother's comfort); at times, it may also be an urgent, threat-induced plea for immediate help. One behavior, then, might serve two different functions and be controlled by different neurochemical pathways. (This conclusion was strengthened for me when I tried to photograph a rhesus infant that had become separated from its mother in the wild, where we are now conducting additional studies. Its persistent, intense coos attracted the mother, along with a pack of protectors. The strategy worked: I retreated rapidly.)

More generally, our chemical studies led us to suspect that the opiate- and benzodiazepine-sensitive circuits both oper-

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RELAXED MOTHER (*left*) barely reacts to the presence of the camera-wielding author, whereas a more sensitive mother (*right*) becomes frightened, as evinced by her "fear grimace." The author hopes explorations of the neural bases for such differences in monkeys will facilitate development of new therapies for excessively anxious humans.

ate during stress; the relative degree of activity changes with the characteristics of a worrisome situation. As the contribution of each pathway is altered, so, too, are the behaviors that appear.

Exactly how neurons in the opiate and benzodiazepine pathways function and how they might cooperate are unclear. But one plausible scenario goes like this: When a young monkey is separated from its mother, opiate-releasing and, consequently, opiate-sensitive neurons become inhibited. Such inhibition gives rise to yearning for the mother and a generalized sense of vulnerability. This reduction of activity in opiate-sensitive pathways enables motor systems in the brain to produce cooing. When a potential predator appears, neurons that secrete endogenous benzodiazepines become suppressed to some degree. This change, in turn, leads to elevated anxiety and the appearance of behaviors and hormonal responses that accompany fear. As the sense of alarm grows, motor areas prepare for fight or flight. The benzodiazepine system may also influence the opiate system, thereby altering cooing during threatening situations.

We are now refining our model of brain function by testing other compounds that bind to opiate and benzodiazepine receptors. We are also examining behavioral responses to substances, such as the neurotransmitter serotonin, that act on other receptors. (Serotonin receptors occur in many brain regions that participate in the expression of fear.) And we are studying the activities of substances that directly control stress hormone production, including corticotropin-releasing hormone, which is found throughout the brain.

In collaboration with Richard J. Davidson, here at Wisconsin, Shelton and I have identified at least one brain region in which the benzodiazepine system exerts its effects. Davidson had shown that the prefrontal cortex of the right hemisphere is unusually active in extremely inhibited children. We therefore wondered whether we would see the same asymmetry in frightened monkeys and whether drugs that reduced fear-related behavior in the animals would dampen right frontal activity.

This time we used mild restraint as a stress. As we anticipated, neuronal firing rose more in the right frontal cortex than in the left. When we delivered diazepam in doses we knew lowered hostility, the drug returned the restraint-induced electrical activity to normal. In other words, the benzodiazepine system influences defensive behavior at least in part by acting in the right prefrontal cortex.

Therapeutic Implications

THESE FINDINGS HAVE therapeutic implications. If human and monkey brains do operate similarly, our data would suggest that benzodiazepines might be most helpful in those adults and children who exhibit elevated electrical activity in the right prefrontal cortex. Because of potential side effects, many clinicians are cautious about delivering antianxiety medications to children over a long time. But administration of such drugs during critical periods of brain development might prove sufficient to alter the course of later development. And behavioral training could possibly teach extremely inhibited youngsters to regulate their benzodiazepine-sensitive systems without having to be medicated. Alternatively, by screening compounds that are helpful in monkeys, investigators might discover new

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drugs that are quite safe for children. As the workings of other fear-modulating neurochemical systems in the brain are elucidated, similar strategies could be applied to manage those circuits.

Our discovery of cues that elicit three distinct sets of fear-related behaviors in rhesus monkeys has thus enabled us to gain insight into the development and regulation of defensive strategies in these animals. We propose that the opiate and benzodiazepine pathways in the prefrontal cortex, the amygdala and the hypothalamus play a major part in determining which strategies are chosen. And we are currently attempting to learn more about the ways in which these and other neural circuits cooperate with one another.

Fearful Temperament

TO FOLLOW UP on the finding that humans with a preponderance of right frontal brain electrical activity are more likely to be anxious, we, along with Davidson, examined individual differences in this measure of brain activity in young monkeys. Similar to the observations in humans, we found that each animal's pattern of frontal brain activity was stable over time, such that animals with extreme asymmetric right frontal activity remained this way as they matured. Recall that we previously documented that a monkey's propensity to freeze is also a relatively stable trait.

Using this brain electrical activity measure, we next screened a large number of monkeys and selected two subsets of animals, those with extreme left frontal activity and those with extreme right frontal activity. Without knowing anything about their behavior, we hypothesized that those animals with extreme right frontal activity would be more fearful and also would have higher levels of cortisol. Based on this single measure of brain activity, this experiment demonstrated that extreme right frontal animals displayed more intense defensive behaviors (freezing and hostility) and had higher levels of cortisol when compared with their extreme left frontal counterparts. Furthermore, the extreme right frontal animals had higher cerebrospinal fluid levels of corticotropin-releasing hormone (CRH), and each individual animal's level of CRH appeared to be relatively stable. CRH not only regulates the release of cortisol but also mediates other fear-related behavioral and physiological responses.

Taken together, these findings led us to describe a fearful/anxious temperament or emotional style that is a relatively stable trait of some individuals. This temperament includes excessive fearfulness and critical physiological components: extreme right frontal brain activity, elevated basal cortisol and increased brain CRH. Evidence from other studies suggests that these characteristics will also hold for humans.

Our next step was to identify the brain regions that underlie these behavioral and physiological features. The first brain region we selected was the amygdala because of its well-known involvement in mediating fear responses and emotions. Researchers such as Joseph E. LeDoux of New York University and Michael Davis of Emory University have extensively explored the functions of this brain region in rodents [see "Emotion, Memory and the Brain," by Joseph E. LeDoux, on page 62]. Yet relatively few studies have used modern neurobiological techniques to examine the role of the amygdala in mediating emotion in primates.

Using techniques developed by David G. Amaral of the University of California at Davis and his colleagues, we were able to inactivate cells selectively in the monkey amygdala, allowing us to explore the role of this structure in mediating fear and anxiety. We expected that monkeys without a functioning amygdala would display marked reductions in defensive behaviors as well as reductions in cortisol and CRH concentrations in the cerebrospinal fluid. We also expected that, as we had observed earlier with diazepam treatment, these monkeys would display a shift in their pattern of frontal brain activity characterized by an increase in left frontal electrical activity and a decrease in the right.

Consistent with earlier studies, we discovered that the monkeys' acute fear responses were blunted. For example, those without a functioning amygdala displayed a blunted withdrawal response when exposed to a snake and a decrease in submissive gestures when placed in the presence of an unfamiliar, threatening larger monkey. Their stress-induced hormonal response was also muted. But we were surprised to observe that these animals did not show deficits in their ability to freeze or display hostile gestures in the human intruder paradigm, nor were the physiological parameters that we believe make up the fearful/anxious temperament affected. Even among monkeys without a functioning amygdala, the magnitude of an individual's defensive response, the pattern of brain electrical activity, and the level of basal cortisol and CRH in the cerebrospinal fluid remained unaffected. In a recent study targeted at a specific region within the amygdala, we found that inactivation of this region blunted, but did not completely ablate, some of the responses associated with the anxious/fearful temperament.

These findings have led us to speculate that in primates, the amygdala serves to mediate acute fear-related responses and that other brain regions are most likely involved in responses that mark stable temperamental traits. Based on human studies and other animal work, we think that the prefrontal cortex may be instrumen-

We have therefore laid the groundwork for deciphering the relative contributions of various brain systems underlying inordinate fear in humans.

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INFANT (*left*) has strayed a short distance from its mother (*center*) and is producing a rudimentary threat face in an attempt to keep a photographer (the author) at bay. Rhesus monkeys become adept at matching their behavior to the severity and type of a threat when they are between nine and 12 weeks old, probably because certain neuronal pathways in three regions of the brain—the prefrontal cortex, amygdala and hypothalamus—reach functional maturity during this same period.

tal in mediating the behavior and physiological aspects of the fearful/anxious temperament.

Studies are now under way to examine a specific region of the prefrontal cortex known as the orbitofrontal cortex. Interconnected with the amygdala, this brain region lies above the eyeballs and is much more prominent in primates than in rodents. Various studies have demonstrated the importance of this area in maintaining long-term, habitual behavioral responses, in modulating emotional responses and in enabling the prediction of the consequences of future behaviors.

Using these techniques in the monkeys in conjunction with human functional brain-imaging studies, we are confident that we and others will be able to characterize the brain circuits and the neurochemicals involved in the expression of adaptive fear and anxiety responses in humans, as well as to understand what is different in the brains of those individuals who suffer from excessive and maladaptive responses. We have therefore laid the groundwork for deciphering the relative contributions of various brain systems underlying inordinate fear in humans. We can envision a time when treatments will be tailored to normalizing the specific signaling pathways that are disrupted in a particular child, thereby sparing that youngster enormous unhappiness later in life. SA

MORE TO EXPLORE

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The brain and the immune system continuously signal each other, often along the same pathways, which may explain how state of mind influences health

The Mind-Body Interaction in Disease

By Esther M. Sternberg and Philip W. Gold

The belief that the mind plays an important role in physical illness goes back to the earliest days of medicine. From the time of the ancient Greeks to the beginning of the 20th century, it was generally accepted by both physician and patient that the mind can affect the course of illness, and it seemed natural to apply this concept in medical treatments of disease. After the discovery of antibiotics, a new assumption arose that treatment of infectious or inflammatory disease requires only the elimination of the foreign organism or agent that triggers the illness. In the rush to discover antibiotics and drugs that cure specific infections and diseases, the fact that the body's own responses can influence susceptibility to disease and its course was largely ignored by medical researchers.

It is ironic that research into infectious and inflammatory disease first led 20th-century medicine to reject the idea that the mind influences physical illness, and now research in the same field—including the work of our laboratories and of our collaborators at the National Institutes of Health—is proving the contrary. New molecular and pharmacological tools have made it possible for us to identify the intricate network that exists between the immune system and the brain, a network that allows the two systems to signal each other continuously and rapidly. Chemicals produced by immune cells signal the brain, and the brain in turn sends chemical signals to restrain the immune system. These same chemical signals also affect behavior and the response to stress. Disruption of this communication network in any way, whether inherited or through drugs, toxic substances or surgery, exacerbates the diseases that these systems guard against: infectious, inflammatory, autoimmune, and associated mood disorders.

IMMUNE RESPONSE can be altered at the cellular level by stress hormones.

The clinical significance of these findings is likely to prove profound. They hold the promise of extending the range of therapeutic treatments available for various disorders, as drugs previously known to work primarily for nervous system problems are shown to be effective against immune maladies, and vice versa. They also help to substantiate the popularly held impression (still discounted in some medical circles) that our state of mind can influence how well we resist or recover from infectious or inflammatory diseases.

The brain's stress response system is activated in threatening situations. The immune system responds automatically to pathogens and foreign molecules. These two response systems are the body's principal means for maintaining an internal steady state called homeostasis. A substantial proportion of human cellular machinery is dedicated to maintaining it.

When homeostasis is disturbed or threatened, a repertoire of molecular, cellular and behavioral responses comes into play. These responses attempt to counteract the disturbing forces in order to reestablish a steady state. They can be specific to the foreign invader or a particular stress, or they can be generalized and nonspecific when the threat to homeostasis exceeds a certain threshold. The adaptive responses may themselves

Updated from The Mysteries of the Mind *(Special Issue, 1997)*

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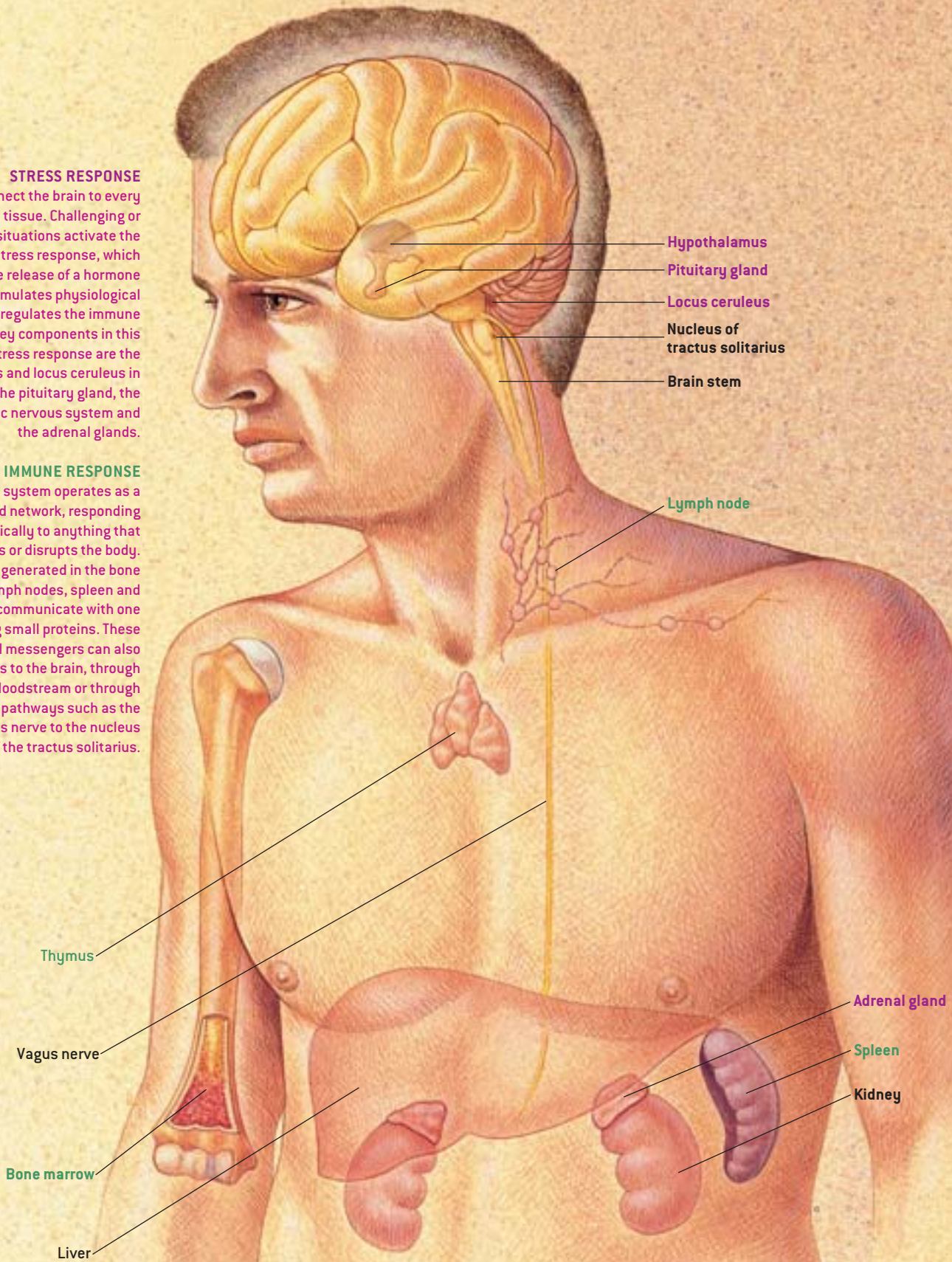
ANATOMY OF THE STRESS AND IMMUNE SYSTEMS

STRESS RESPONSE

Nerves connect the brain to every organ and tissue. Challenging or threatening situations activate the brain's stress response, which involves the release of a hormone that stimulates physiological arousal and regulates the immune system. Key components in this stress response are the hypothalamus and locus ceruleus in the brain, the pituitary gland, the sympathetic nervous system and the adrenal glands.

IMMUNE RESPONSE

The immune system operates as a decentralized network, responding automatically to anything that invades or disrupts the body. Immune cells generated in the bone marrow, lymph nodes, spleen and thymus communicate with one another using small proteins. These chemical messengers can also send signals to the brain, through either the bloodstream or through nerve pathways such as the vagus nerve to the nucleus of the tractus solitarius.



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turn into stressors capable of producing disease. We are just beginning to understand the interdependence of the brain and the immune system, how they help to regulate and counterregulate each other and how they themselves can malfunction and produce disease.

The stress response promotes physiological and behavioral changes in threatening or taxing situations. For instance, when we are facing a potentially life-threatening situation, the brain's stress response goes into action to enhance our focused attention, our fear and our fight-or-flight response, while inhibiting behaviors, such as feeding, sex and sleep, that might lessen the chance of immediate survival. The stress response, however, must be regulated to be neither excessive nor suboptimal; otherwise, disorders of arousal, thought and feeling emerge.

The immune system's job is to bar foreign pathogens from the body and to recognize and destroy those that penetrate its shield. The immune system must also neutralize potentially dangerous toxins, facilitate repair of damaged or worn tissues, and dispose of abnormal cells. Its responses are so powerful that they require constant regulation to ensure that they are neither excessive nor indiscriminate and yet remain effective. When the immune system escapes regulation, autoimmune and inflammatory diseases or immune deficiency syndromes result.

The immune and central nervous systems appear, at first glance, to be organized in very different ways. The brain is usually regarded as a centralized command center, sending and receiving electrical signals along fixed pathways, much like a telephone network. In contrast, the immune system is decentralized, and its organs (spleen, lymph nodes, thymus and bone marrow) are located throughout the body. The classical view is that the immune system communicates by releasing immune cells into the bloodstream that travel to new locations to deliver their messages or to perform other functions.

The central nervous and immune systems, however, are more similar than different in their modes of receiving, recognizing and integrating various signals and in their structural design for accomplishing these tasks. Both the central nervous system and the immune system possess "sensory" elements, which receive information from the environment and other parts of the body, and "motor" elements, which carry out an appropriate response.

Cross Communication

BOTH SYSTEMS also rely on chemical mediators for communication. Electrical signals along nerve pathways, for instance, are converted to chemical signals at the synapses between neurons. The chemical messengers produced by immune cells communicate not only with other parts of the immune system but also with the brain and nerves. Chemicals released by nerve cells can act as signals to immune cells. Hormones from the body travel to the brain in the bloodstream, and the brain itself makes hormones. Indeed, the brain is perhaps the most prolific endocrine organ in the body and produces many hormones that act both on the brain and on tissues throughout the body.

A key hormone shared by the central nervous and immune systems is corticotropin-releasing hormone (CRH); produced in the hypothalamus and several other brain regions, it unites the stress and immune responses. The hypothalamus releases CRH into a specialized bloodstream circuit that conveys the hormone to the pituitary gland, which lies just beneath the brain. CRH causes the pituitary to release adrenocorticotropin hormone (ACTH) into the bloodstream, which stimulates the adrenal glands to produce cortisol, the best-known stress hormone.

Cortisol is a steroid hormone that increases the rate and strength of heart contractions, sensitizes blood vessels to the actions of norepinephrine (an adrenaline-like hormone) and affects many metabolic functions—actions that help the body meet a stressful situation. In addition, cortisol is a potent immunoregulator and anti-inflammatory agent. It plays a crucial role in preventing the immune system from overreacting to injuries and damaging tissues. Furthermore, cortisol inhibits the release of CRH by the hypothalamus—which keeps this component of the stress response under control. Thus, CRH and cortisol directly link the body's brain-regulated stress response and its immune response.

CRH-secreting neurons of the hypothalamus send fibers to regions in the brain stem that help to regulate the sympathetic nervous system, as well as to another brain stem area called the locus ceruleus. The sympathetic nervous system, which mobilizes the body during stress, also innervates immune organs, such as the thymus, lymph nodes and spleen, and helps to control inflammatory responses throughout the body. Stimulation of the locus ceruleus leads to behavioral arousal, fear and enhanced vigilance.

Perhaps even more important for the

The ADAPTIVE RESPONSES may themselves turn into stressors capable of PRODUCING DISEASE.

THE AUTHORS

ESTHER M. STERNBERG and *PHILIP W. GOLD* carry out their research on stress and immune systems at the National Institute of Mental Health. Sternberg is chief of the section on neuroendocrine immunology and behavior and director of the Integrative Neural Immune Program, and Gold is chief of the clinical neuroendocrinology branch. Sternberg received her M.D. from McGill University. Her work on the mechanisms and molecular basis of neural immune communication has led to a growing recognition of the importance of mind-body interaction. She is also the author of *The Balance Within: The Science Connecting Health and Emotions* (2000). Before joining the NIMH in 1974, Gold received his medical training at Duke University and Harvard University. He and his group were among the first to introduce data implicating corticotropin-releasing hormone and its related hormones in the pathophysiology of melancholic and atypical depression and in the mechanisms of action of antidepressant drugs.

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induction of fear-related behaviors is the amygdala, where inputs from the sensory regions of the brain are charged as stressful or not. CRH-secreting neurons in the central nucleus of the amygdala send fibers to the hypothalamus, the locus ceruleus, and to other parts of the brain stem. These CRH-secreting neurons are targets of messengers released by immune cells during an immune response. By recruiting the CRH-secreting neurons, the immune signals not only activate cortisol-mediated restraint of the immune response but also induce behaviors that assist in recovery from illness or injury. CRH-secreting neurons also have connections with hypothalamic regions that regulate food intake and reproductive behavior. In addition, other hormonal and nerve systems—such as the thyroid, growth and female sex hormones, and the sympathomedullary pathways (connections of the sympathetic nervous system and medulla)—influence interactions between the brain and the immune system.

Immune System Signals

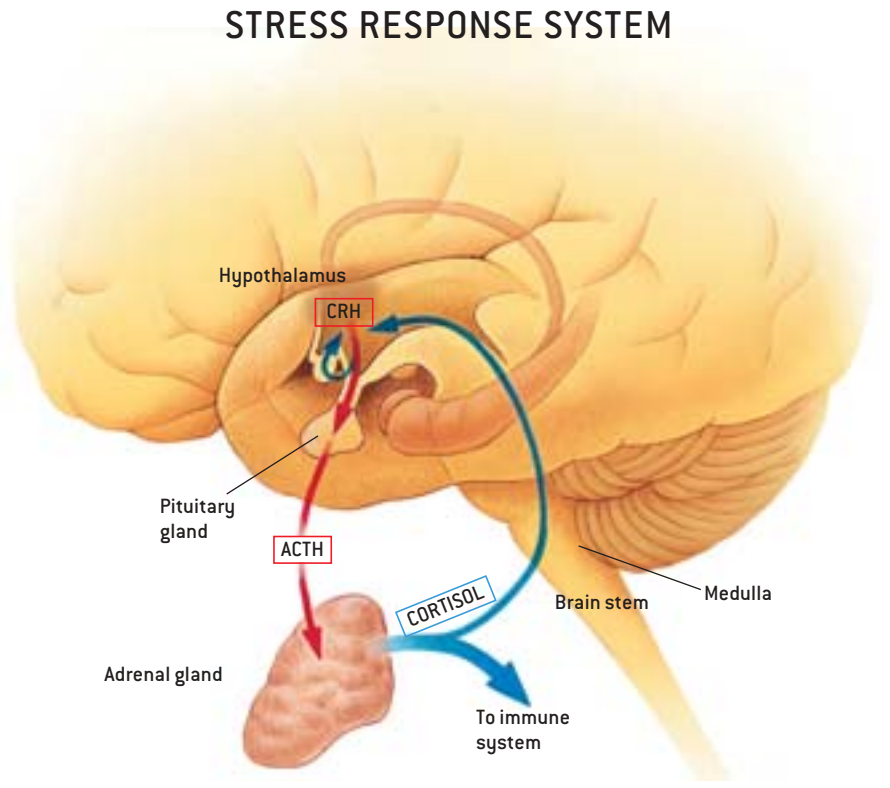
THE IMMUNE RESPONSE is an elegant and finely tuned cascade of cellular events aimed at ridding the body of foreign substances, bacteria and viruses. One of the major discoveries of contemporary immunology is that white blood cells produce small proteins that indirectly coordinate the responses of other parts of the immune system to pathogens.

For example, the protein interleukin-1 (IL-1) is made by a type of white blood cell called a monocyte or macrophage. IL-1 stimulates another type of white blood cell, the lymphocyte, to produce interleukin-2 (IL-2), which in turn induces lymphocytes to develop into mature immune cells. Some mature lymphocytes, called plasma cells, make antibodies that fight infection, whereas others, the cytotoxic lymphocytes, kill viruses directly. Other interleukins mediate the activation of immune cells that are involved in allergic reactions.

The interleukins were originally named for what was considered to be their primary function: communication among ("inter-") the white blood cells ("leukins"). But interleukins also act as chemical signals among immune cells and many other types of cells and organs, including parts of the brain. Cytokines is the more general term for biological molecules that many different kinds of cells use to communicate. Each cytokine is a distinct protein molecule, encoded by a separate gene, that targets a particular cell type. A cytokine can either stimulate or inhibit a response depending on the presence of other cytokines or other stimuli and the current state of metabolic activity. This flexibility allows the immune system to take the most appropriate actions to stabilize the local cellular environment and to maintain homeostasis.

Cytokines from the body's immune system can send signals to the brain in several ways. Ordinarily, a "blood-brain barrier" shields the central nervous system from potentially dangerous molecules in the bloodstream. During inflammation or illness, however, this barrier becomes more permeable, and cytokines may be carried across into the brain with nutrients from the blood. Certain cytokines, on the other hand, readily pass through leaky areas in the blood-brain barrier at any time. But cytokines do not have to cross the blood-brain barrier to exert their effects. Cytokines can attach to their receptors in the lining of blood vessels in the brain and stimulate the release of secondary chemical signals in the brain tissue around the blood vessels.

Cytokines can also signal the brain via direct nerve routes, such as the vagus nerve, which innervates the heart, stomach, small intestine and other organs of the abdominal cavity. Injection of IL-1 into the abdominal cavity activates the nucleus of the tractus solitarius, the principal region of the brain stem for receipt of visceral sensory signals. Cutting the vagus nerve blocks activation of this brain



HPA AXIS—the interplay among the hypothalamus, the pituitary and the adrenal glands—is a central component of the brain's neuroendocrine response to stress. The hypothalamus, when stimulated, secretes corticotropin-releasing hormone (CRH) into the hypophyseal portal system, which supplies blood to the anterior pituitary. CRH stimulates the pituitary (*red arrows show stimulatory pathways*) to secrete adrenocorticotropin hormone (ACTH) into the bloodstream. ACTH causes the adrenal glands to release cortisol, the classic stress hormone that arouses the body to meet a challenging situation. But cortisol then modulates the stress response (*blue arrows indicate inhibitory effects*) by acting on the hypothalamus to inhibit the continued release of CRH. Also a potent immunoregulator, cortisol acts on many parts of the immune system to prevent it from overreacting and harming healthy cells and tissue.

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nucleus by IL-1. Sending signals along nerve routes is the most rapid mechanism—on the order of milliseconds—by which cytokines signal the brain.

Activation of the brain by cytokines from the peripheral parts of the body induces behaviors of the stress response, such as anxiety and cautious avoidance, that keep an individual out of harm's way until full healing occurs. Anyone who has experienced lethargy and excess sleepiness during an illness will recognize this set of responses as "sickness behavior."

brain tissue of patients living with AIDS, concentrated in areas around the giant macrophages that invade the patients' brain tissue. Immune factors, however, are not always toxic to neurons. Specific activated T lymphocytes play an important role in preventing neuronal cell death after injury. This discovery is leading to new approaches to treating and preventing paralysis following spinal cord injury.

Any disruption of communication between the brain and the immune system leads to greater susceptibility to inflammatory disease and, frequently, to increased immune complications. For instance, animals whose brain-immune communications have been disrupted (through surgery or drugs) are highly liable to lethal complications of inflammatory diseases and infectious diseases.

Susceptibility to inflammatory disease that is associated with genetically impaired stress response can be found across species—in rats, mice, chickens and, though the evidence is less direct, humans. For instance, the Lewis strain of rat is naturally prone to many inflammatory diseases because of a severe impairment of its HPA (for hypothalamus, pituitary and adrenal) axis, which greatly diminishes CRH secretion in response to stress. In contrast, the hyperresponsive HPA axis in the Fischer strain of rat provides it with a strong resistance to inflammatory disease.

Evidence of a causal link between an impaired stress response and susceptibility to inflammatory disease comes from pharmacological and surgical studies. Pharmacological intervention such as treatment with a drug that blocks cortisol receptors enhances autoimmune inflammatory disease. Injecting low doses of cortisol into disease-susceptible rats enhances their resistance to inflammation. Strong evidence comes from surgical intervention. Removal of the pituitary gland or the adrenal glands from rats that are normally resistant to inflammatory disease renders them highly susceptible. Further proof comes from studies in which the transplantation of hypothalamic tissue from disease-resistant rats into the brain of susceptible rats improves their resistance to peripheral inflammation.

These animal studies demonstrate that disruption of the brain's stress response enhances the body's response to inflammatory disease, and reconstitution of the stress response reduces susceptibility to inflammation. One implication of these findings is that disruption of the brain-immune communication system by inflammatory, toxic or infectious agents could contribute to some of the variations in the course of the immune system's inflammatory response.

The IMMUNE RESPONSE is an elegant and finely tuned cascade of cellular events aimed at ridding the body of FOREIGN SUBSTANCES.

Indeed, patients receiving cytokine treatment for immunosuppression in cancer and AIDS may experience symptoms of depression and even suicidality. These symptoms can be prevented by pretreatment with antidepressants.

Neurons and nonneuronal brain cells also produce cytokines. Cytokines in the brain regulate nerve cell growth and death and can be recruited by the immune system to stimulate the release of CRH. Some have proposed that brain cytokines may play a role in symptoms of depression in the absence of known sickness or infection.The IL-1 cytokine system in the brain is currently the best understood—all its components have been identified, including receptors and a naturally occurring antagonist that binds to IL-1 receptors without activating them. The anatomical and cellular locations of such cytokine circuitry are being mapped out in detail, and this knowledge will aid researchers in designing drugs that block or enhance the actions of such circuits and the functions they regulate.

Excessive amounts of cytokines in the brain can be toxic to nerves. In genetically engineered mice, inserted genes that overexpress cytokines produce neurotoxic effects. Some of the neurological symptoms of AIDS in humans may also be caused by overexpression of certain cytokines in the brain. High levels of IL-1 and other cytokines have been found in the

CRH and Depression

ALTHOUGH THE ROLE of the stress response in inflammatory disease in humans is more difficult to prove, there is growing evidence that a wide variety of such diseases are associated with impairment of the HPA axis and lower levels of CRH secretion, which ultimately results in a hyperactive immune system. Furthermore, patients with a mood disorder called atypical depression also have a blunted stress response and impaired CRH function, which leads to lethargy, fatigue, increased sleep and increased eating that often results in weight gain.

Patients with other illnesses characterized by lethargy and fatigue, such as chronic fatigue syndrome, fibromyalgia and seasonal affective disorder (SAD), exhibit features of both depression and a hyperactive immune system. A person with chronic fatigue syndrome classically manifests debilitating lethargy or fatigue lasting six months or longer with no demonstrable medical cause, as well as feverishness, aches in joints and muscles, allergic symptoms and higher levels of antibodies to a variety of viral antigens (including Epstein-Barr virus).

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Patients with fibromyalgia suffer from muscle aches, joint pains and sleep abnormalities, symptoms similar to early, mild rheumatoid arthritis. Both these illnesses are associated with a fatigue like that in atypical depression. SAD, which usually occurs in winter, is typified by lethargy, fatigue, increased food intake and increased sleep, symptoms similar to those of atypical depression.

A deficiency of CRH could contribute to lethargy in patients with chronic fatigue syndrome. Injection of CRH into these patients causes a delayed and blunted ACTH secretion by the HPA axis. That same response is also seen in patients whose hypothalamus has been injured or who have a tumor. Also, fatigue and hyperactivity of the immune response are associated with cortisol deficiency, which occurs when CRH secretion decreases. The hormone levels and responses in patients with fatigue syndromes suggest—but do not prove—that their HPA axis functions are impaired, resulting in a decrease in CRH and cortisol secretion and an increase in immune system activity. Together these findings indicate that human illness characterized by fatigue and hyperimmunity could possibly be treated by drugs that mimic CRH actions in the brain.

In contrast, the classic form of depression, melancholia, is actually not a state of inactivation and suppression of thought and feeling; rather it presents as an organized state of anxiety. The anxiety of melancholia is chiefly about the self. Melancholic patients feel impoverished and defective and often express hopelessness about the prospects for their unworthy selves in either love or work. The anxious hyperarousal of melancholic patients also manifests as a pervasive sense of vulnerability.

Melancholic patients also show behavioral alterations suggestive of physiological hyperarousal. They characteristically suffer from insomnia (usually early-morning awakening) and experience inhibition of eating, sexual activity and menstruation. One of the most widely found biological abnormalities in patients with melancholia is that of sustained hypersecretion of cortisol.

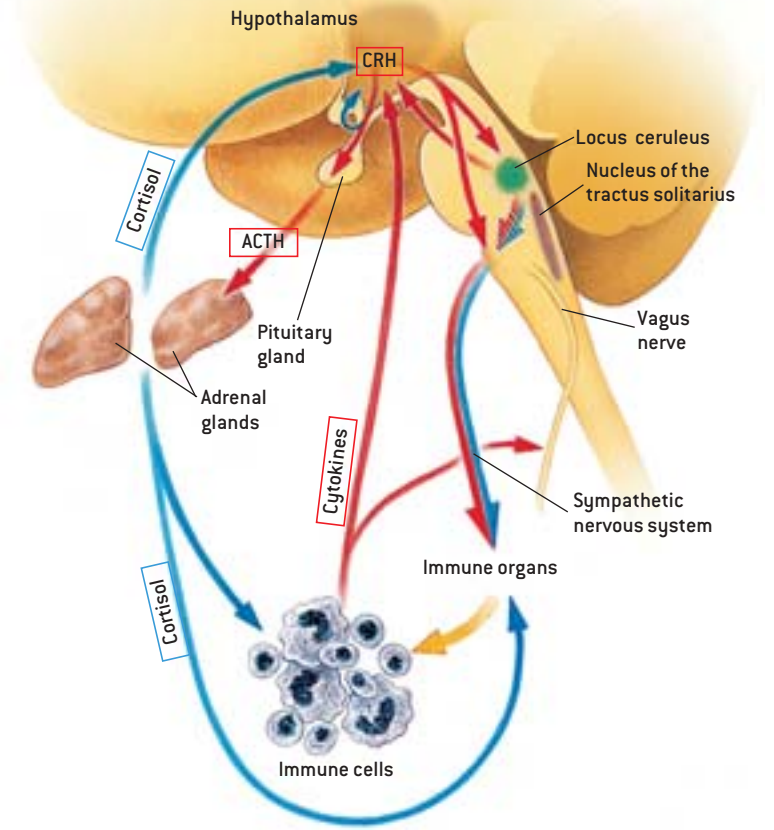
Many studies have been conducted on patients with major depression to determine whether the excessive level of cortisol associated with depression correlates with suppressed immune responses. Some have found a correlation between hypercortisolism and immunosuppression; others have not. Because depression can have a variety of mental and biochemical causes, only some depressed patients may be immunosuppressed.

The excessive secretion of cortisol in melancholic patients is predominantly the result of hypersecretion of CRH, caused by a defect in or above the hypothalamus. Thus, the clinical and biochemical manifestations of melancholia reflect a generalized stress response that has escaped the usual counterregulation, remaining stuck in the "on" position.

The effects of tricyclic antidepressant drugs on components of the stress response support the concept that melancholia is associated with a chronic stress response. In rats, regular, but not acute, administration of the tricyclic antidepressant imipramine significantly lowers the levels of CRH precursors in the hypothalamus. Imipramine given for two months to healthy people with normal cortisol levels causes a gradual and sustained decrease in CRH secretion and other HPA axis functions, indicating that down-regulation of important components of the stress response is an intrinsic effect of imipramine.

Depression is also associated with inflammatory disease. About 20 percent of patients with rheumatoid arthritis develop clinical depression. A questionnaire commonly used by clinicians to diagnose depression contains about a dozen questions that are almost always answered affirmatively by patients with arthritis.

INTERACTION OF THE BRAIN AND IMMUNE SYSTEM



BRAIN AND IMMUNE SYSTEM can either stimulate (*red arrows*) or inhibit (*blue arrows*) each other. Immune cells produce cytokines (chemical signals) that stimulate the hypothalamus through the bloodstream or via nerves elsewhere in the body. The hormone CRH, produced in the hypothalamus, activates the HPA axis. The release of cortisol tunes down the immune system. CRH, acting on the brain stem, stimulates the sympathetic nervous system, which innervates immune organs and regulates inflammatory responses throughout the body. Disruption of these communications in any way leads to greater susceptibility to disease and immune complications.

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In the past, the association between an inflammatory disease and stress was considered by doctors to be secondary to the chronic pain and debilitation of the disease. The recent discovery of the common underpinning of the immune and stress responses may provide an explanation of why a patient can be susceptible to both inflammatory disease and depression. The hormonal dysregulation that underlies both inflammatory disease and depression can lead to either illness, depending on whether the perturbing stimulus is pro-inflammatory or psychologically stressful. That may explain why the waxing and waning of depression in arthritic patients does not always coincide with inflammatory flare-ups.

The popular belief that stress exacerbates inflammatory illness and that relaxation or removal of stress ameliorates it may indeed have a basis in fact. The interactions of the stress and immune systems and the hormonal responses they have in common could explain how conscious attempts to tone down responsivity to stress could affect immune responses.

Genetic Factors

HOW MUCH of the responsivity to stress is genetically determined and how much can be consciously controlled is not known. The set point of the stress response is to some extent genetically determined. In addition, factors in early development, learning, and later experiences contribute to differences in stress responsiveness. An event that is physiologically highly stressful to one individual may be much less so to another, depending on the sum of each person's genetic tendency to hormonal reactivity and their previous experience. The degree to which stress could precipitate or exacerbate disease would then depend not only on the intensity and duration of the stressful stimulus but also on the person's learned perception of the event as stressful and on the set point of the stress system.

Psychological stress can affect an individual's susceptibility to infectious diseases. The regulation of the immune system by the neurohormonal stress system provides a biological basis for understanding how stress might affect these diseases. Thus, stress hormones released from the brain, cortisol from the adrenal glands, and nerve chemicals released from nerve endings (adrenalinlike molecules norepinephrine and epinephrine) all modify the ability of immune cells to fight infectious agents and foreign molecules.

There is evidence that stress does affect human immune responses to viruses and bacteria. In studies with volunteers given a standard dose of the common cold virus (rhinovirus), individuals who are simultaneously exposed to stress show more viral particles and produce more mucus than do nonstressed individuals. Medical students receiving hepatitis vaccination during their final exams do not develop full protection against hepatitis. These findings have important implications for public health. People who are vaccinated during periods of stress might be less likely to develop full antibody protection. Chronic stress also prolongs wound healing.

New research shows that at physiological concentrations and under certain conditions the stress hormone cortisol not only is immunosuppressive but also may enhance certain aspects of immune function. Furthermore, each part of the stress response—the brain-hormonal, the adrenalinlike nerve and the adrenal gland adrenalin—is regulated independently, depending on the nature of the stressful stimulus. This specific nature of the stress response explains how different kinds and patterns of stress affect illness differently. Therefore, whereas chronic stress is generally immunosuppressive, acute stress can enhance cell-mediated immunity and exacerbate contact dermatitis types of allergic skin reactions. Furthermore, animal studies show that social stress and physical stress have different effects on infection with different viruses, such as herpes and influenza virus.

Animal studies provide further evidence that stress affects the course and severity of viral illness, bacterial disease and septic shock. Stress in mice worsens the severity of influenza infection through both the HPA axis and the sympathetic nervous system. Animal studies suggest that neuroendocrine mechanisms could play a similar role in infections with other viruses, including HIV, and provide a mechanism for understanding clinical observations that stress may exacerbate the course of AIDS. Stress, through cortisol, increases the susceptibility of mice to infection with mycobacteria, the bacteria that causes tuberculosis. It has been shown that an intact HPA axis protects rats against the lethal septic effects of salmonella bacteria. Finally, new understanding of interactions of the immune and stress responses can help explain the puzzling observation that classic psychological conditioning of animals can influence their immune responses. For example, working with mice and rats, Robert Ader and Nicholas Cohen of the University of Rochester paired saccharin-flavored water with an immunosuppressive drug. Eventually the saccharin alone produced a decrease in immune function similar to that of the drug.

Social Stresses

STRESS NOT ONLY IS personal but is perceived through the prism of social interactions. These interactions can either add to or lessen psychological stress and affect our hormonal responses to it, which in turn can alter immune responses. Thus, the social-psychological stresses that we experience can affect our susceptibility to inflammatory and infectious diseases as well as the course of these and other diseases. For instance, in humans, loneliness is associated with a "threat," or adrenalinlike pattern of activation of the stress response and high blood pressure, whereas exercising is associated with a "challenge" pattern of high blood

Psychological STRESS CAN AFFECT an individual's SUSCEPTIBILITY to infectious diseases.

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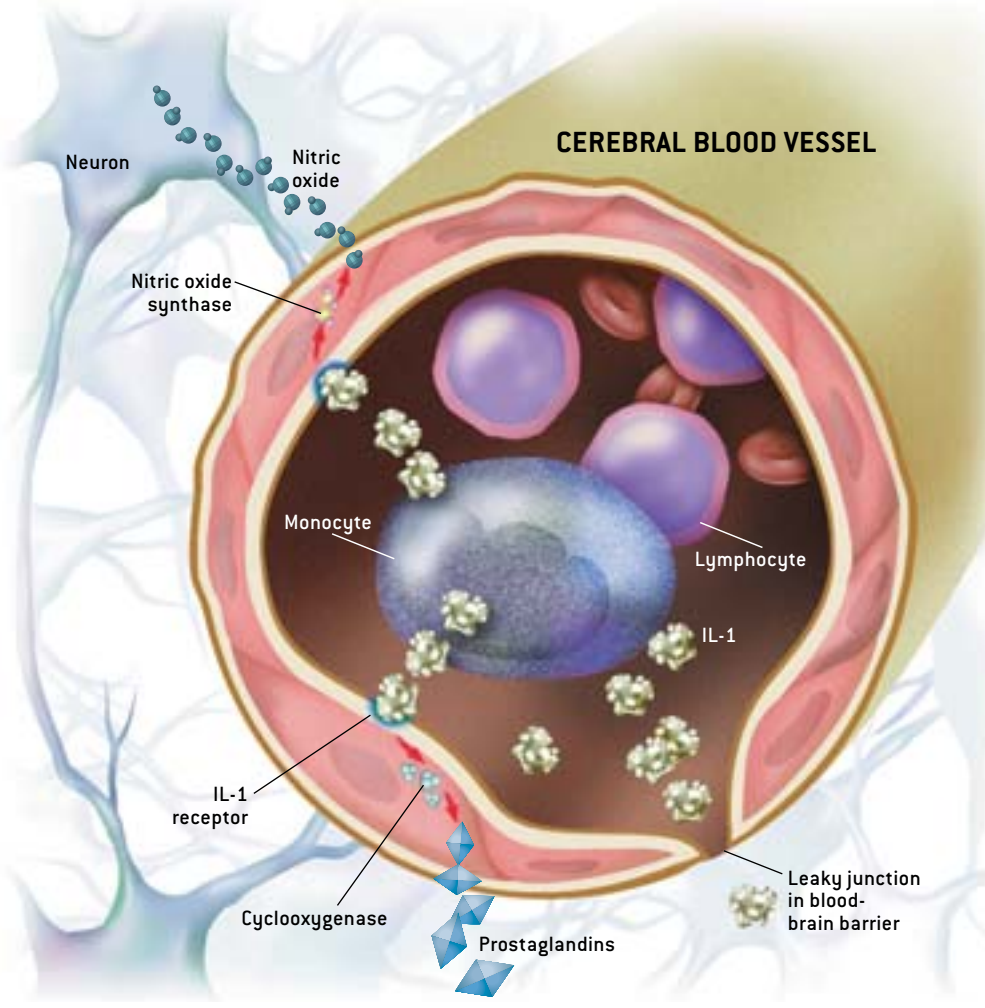

IMMUNE SIGNALS TO THE BRAIN via the bloodstream can occur directly or indirectly. Immune cells such as monocytes, a type of white blood cell, produce a chemical messenger called interleukin-1 (IL-1), which ordinarily will not pass through the blood-brain barrier. But certain cerebral blood vessels contain leaky junctions, which allow IL-1 molecules to pass into the brain. There they can activate the HPA axis and other neural systems. IL-1 also binds to receptors on the endothelial cells that line cerebral blood vessels. This binding can cause enzymes in the cells to produce nitric oxide or prostaglandins, which diffuse into the brain and act directly on neurons.

flow and cardiac output. Studies have shown that people exposed to chronic social stresses for more than two months have increased susceptibility to the common cold.

Other studies have shown that the immune responses of long-term caregivers, such as spouses of Alzheimer's patients, become blunted. Immune responses during marital discord are also blunted in the spouse (usually the wife) who experiences the greatest amount of stress and feelings of helplessness. In such a scenario, studies have found that the levels of stress hormones are elevated in the affected spouse.

On the other hand, a positive supportive environment of extensive social networks or group psychotherapy can enhance immune response and resistance to disease—even cancer. Some studies have shown that women with breast cancer, for instance, who receive strong, positive social support during their illness have significantly longer life spans than women without such support.

For centuries, taking the cure at a mountain sanatorium or a hot-springs spa was the only available treatment for many chronic diseases. New understanding of the communication between the brain and immune system provides a physiological explanation of why such cures sometimes worked. Disruption of this communication network leads to an increase in susceptibility to disease and can worsen the course of the illness. Restoration of this communication system, whether through pharmacological agents or the relaxing effects of a spa, can be the first step on the road to recovery.

A corollary of these findings is that psychoactive drugs may be used to treat some inflammatory diseases, and drugs that affect the immune system may be useful in treating some psychiatric disorders. There is growing evidence that our view of ourselves and others, our style of handling stresses, and our genetic makeup can affect the immune system. Similarly, there is good evidence that diseases associated with chronic inflammation significantly affect one's mood or level of anxiety. Finally, these findings suggest that classification of illnesses into medical and psychiatric specialties, and the boundaries that have demarcated mind and body, are artificial. SA

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LAURIE GRACE

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the puzzle of conscious experience

WE ARE AT LAST PLUMBING ONE OF THE MOST PROFOUND MYSTERIES OF EXISTENCE. BUT KNOWLEDGE OF THE BRAIN ALONE MAY NOT GET TO THE BOTTOM OF IT

BY DAVID J. CHALMERS

CONSCIOUSNESS, the subjective experience of an inner self, poses one of the greatest challenges to neuroscience. Even a detailed knowledge of the brain's workings and the neural correlates of consciousness may fail to explain how or why human beings have self-aware minds.

Updated from the December 1995 issue

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CONSCIOUS experience is at once the most familiar thing in the world and the most mysterious. There is nothing we know about more directly than consciousness, but it is extraordinarily hard to reconcile it with everything else we know. Why does it exist? What does it do? How could it possibly arise from neural processes in the brain? These questions are among the most intriguing in all of science.

From an objective viewpoint, the brain is relatively comprehensible. When you look at this page, there is a whir of processing: photons strike your retina, electrical signals are passed up your optic nerve and between different areas of your brain, and eventually you might respond with a smile, a perplexed frown or a remark. But there is also a subjective aspect. When you look at the page, you are conscious of it, directly experiencing the images and words as part of your private, mental life. You have vivid impressions of the colors and shapes of the images. At the same time, you may be feeling some emotions and forming some thoughts. Together such experiences make up consciousness: the subjective, inner life of the mind.

For many years, consciousness was shunned by researchers studying the brain and the mind. The prevailing view was that science, which depends on objectivity, could not accommodate something as subjective as consciousness. The behaviorist movement in psychology, dominant earlier in this century, concentrated on external behavior and disallowed any talk of internal mental processes. Later, the rise of cognitive science focused attention on processes inside the head. Still, consciousness remained off-limits, fit only for late-night discussion over drinks.

Over the past several years, however, an increasing number of neuroscientists, psychologists and philosophers have been rejecting the idea that consciousness cannot be studied and are attempting to delve into its secrets. As might be expected of a field so new, there is a tangle of diverse and conflicting theories, often using basic concepts in incompatible ways. To help unsnarl the tangle, philosophical reasoning is vital.

The myriad views within the field range from reductionist theories, according to which consciousness can be explained by the standard methods of neuroscience and psychology, to the position of the so-called mysterians, who say we will never understand consciousness at all. I believe that on close analysis both of these views can be seen to be mistaken and that the truth lies somewhere in the middle.

Against reductionism I will argue that the tools of neuroscience cannot provide a full account of conscious experience, although they have much to offer. Against mysterianism I will hold that consciousness might be explained by a new kind of theory. The full details of such a theory are still out of reach, but careful reasoning and some educated inferences can reveal something of its general nature. For example, it will probably involve new fundamental laws, and the concept of information may play a central role. These faint glimmerings suggest that a theory of consciousness may have startling consequences for our view of the universe and of ourselves.

A theory of consciousness may have startling consequences for our view of the universe and of ourselves.

PEERING into our inner selves can be frustrating.

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The Hard Problem

RESEARCHERS use the word "consciousness" in many different ways. To clarify the issues, we first have to separate the problems that are often clustered together under the name. For this purpose, I find it useful to distinguish between the "easy problems" and the "hard problem" of consciousness. The easy problems are by no means trivial—they are actually as challenging as most in psychology and biology—but it is with the hard problem that the central mystery lies.

The easy problems of consciousness include the following: How can a human subject discriminate sensory stimuli and react to them appropriately? How does the brain integrate information from many different sources and use this information to control behavior? How is it that subjects can verbalize their internal states? Although all these questions are associated with consciousness, they all concern the objective mechanisms of the cognitive system. Consequently, we have every reason to expect that continued work in cognitive psychology and neuroscience will answer them.

The hard problem, in contrast, is the question of how physical processes in the brain give rise to subjective experience. This puzzle involves the inner aspect of thought and perception: the way things feel for the subject. When we see, for example, we experience visual sensations, such as that of vivid blue. Or think of the ineffable sound of a distant oboe, the agony of an intense pain, the sparkle of happiness or the meditative quality of a moment lost in thought. All are part of what

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BLACK-AND-WHITE PHOTOGRAPH BY DAN WAGNER; DIGITAL COMPOSITION BY TOM DRAPER DESIGN

ISOLATED NEUROSCIENTIST in a black-and-white room knows everything about how the brain processes colors but does not know what it is like to see them. By itself, empirical knowledge of the brain does not yield complete knowledge of conscious experience.

I call consciousness. It is these phenomena that pose the real mystery of the mind.

To illustrate the distinction, consider a thought experiment devised by the Australian philosopher Frank Jackson. Suppose that Mary, a neuroscientist in the 23rd century, is the world's leading expert on the brain processes responsible for color vision. But Mary has lived her whole life in a black-and-white room and has never seen any other colors. She knows everything there is to know about physical processes in the brain—its biology, structure and function. This understanding enables her to grasp all there is to know about the easy problems: how the brain discriminates stimuli, integrates information and produces verbal reports. From her knowledge of color vision, she knows how color names correspond with wavelengths on the light spectrum. But there is still something crucial about color vision that Mary does not know: what it is like to experience a color such as red. It follows that there are facts about conscious experience that cannot be deduced from physical facts about the functioning of the brain.

Indeed, nobody knows why these physical processes are accompanied by conscious experience at all. Why is it that when our brains process light of a certain wavelength, we have an experience of deep purple? Why do we have any experience at all? Could not an unconscious automaton have performed the same tasks just as well? These are questions that we would like a theory of consciousness to answer.

Is Neuroscience Enough?

I AM NOT DENYING that consciousness arises from the brain. We know, for example, that the subjective experience of vision is closely linked to processes in the visual cortex. It is the link itself that perplexes, however. Remarkably, sub-

THE AUTHOR

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jective experience seems to emerge from a physical process. But we have no idea how or why this is.

Given the flurry of recent work on consciousness in neuroscience and psychology, one might think this mystery is starting to be cleared up. On closer examination, however, it turns out that almost all the current work addresses only the easy problems of consciousness. The confidence of the reductionist view comes from the progress on the easy problems, but none of this makes any difference where the hard problem is concerned.

Consider the hypothesis put forward by neurobiologists Francis Crick of the Salk Institute for Biological Studies in San Diego and Christof Koch of the California Institute of Technology. They suggest that consciousness may arise from certain oscillations in the cerebral cortex, which become synchronized as neurons fire 40 times per second. Crick and Koch believe the phenomenon might explain how different attributes of a single perceived object (its color and shape, for example), which are processed in different parts of the brain, are merged into a coherent whole. In this theory, two pieces of information become bound together precisely when they are represented by synchronized neural firings.

The hypothesis could conceivably elucidate one of the easy problems about how information is integrated in the brain. But why should synchronized oscillations give rise to a visual experience, no matter how much integration is taking place? This question involves the hard problem, about which the theory has nothing to offer. Indeed, Crick and Koch are agnostic about whether the hard problem can be solved by science at all [*see box below*].

The same kind of critique could be applied to almost all the recent work on consciousness. In his 1991 book *Consciousness Explained*, philosopher Daniel C. Dennett laid out a sophisticated theory of how numerous independent processes in the brain combine to pro-

WHY NEUROSCIENCE MAY BE ABLE TO EXPLAIN CONSCIOUSNESS

By Francis Crick and Christof Koch

We believe that at the moment the best approach to the problem of explaining consciousness is to concentrate on finding what is known as the neural correlates of consciousness—the processes in the brain that are most directly responsible for consciousness. By locating the neurons in the cerebral cortex that correlate best with consciousness, and figuring out how they link to neurons elsewhere in the brain, we may come across key insights into what David J. Chalmers calls the hard problem: a full accounting of the manner in which subjective experience arises from these cerebral processes.

We commend Chalmers for boldly recognizing and focusing on the hard problem at this early stage, although we are not as enthusiastic about some of his thought experiments. As we see it, the hard problem can be broken down into several questions: Why do we experience anything at all? What leads to a particular conscious experience (such as the blueness of blue)? Why are some aspects of subjective experience impossible to convey to other people (in other words, why are they private)? We believe we have an answer to the last problem and a suggestion about the first two, revolving around a phenomenon known as explicit neuronal representation.

What does "explicit" mean in this context? Perhaps the best way to define it is with an example. In response to the image of a face, say, ganglion cells fire all over the retina, much like the pixels on a television screen, to generate an implicit representation of the face. At the same time, they can also respond to a great many other features in the image, such as shadows, lines, uneven lighting and so on. In contrast, some neurons high in the hierarchy of the visual cortex respond mainly to the face or even to the face viewed at a particular angle. Such neurons help the brain represent the face in an explicit manner. Their loss, resulting from a stroke or some other brain injury, leads to prosopagnosia, an individual's inability to recognize familiar faces consciously—even his or her own, although the person can still identify a face as a face. Similarly, damage to other parts of the visual cortex can cause someone to lose the ability to experience color, while still seeing in shades of black and white, even though there is no defect in the color receptors in the eye.

At each stage, visual information is reencoded, typically in a semihierarchical manner. Retinal ganglion cells respond to a spot of light. Neurons in the primary visual cortex are most adept at responding to lines or edges; neurons higher up might prefer a moving contour. Still higher are those that respond to faces and other familiar objects. On top are those that project to pre-motor and motor structures in the brain, where they fire the neurons that initiate such actions as speaking or avoiding an oncoming automobile.

Chalmers believes, as we do, that the subjective aspects of an experience must relate closely to the firing of the neurons corresponding to those aspects (the neural correlates). He describes a well-known thought experiment, constructed around a hypothetical neuroscientist, Mary, who specializes in color perception but has never seen a color. We believe the reason Mary does not know what it is like to see a color, however, is that she has never had an explicit neural representation of a color in her brain, only of the words and ideas associated with colors.

In order to describe a subjective visual experience, the information has to be transmitted to the motor output stage of the brain, where it becomes available for verbalization or other actions. This transmission always involves reencoding the information, so that the explicit information expressed by the motor neurons is related, but not identical, to the explicit

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duce a coherent response to a perceived event. The theory might do much to explain how we produce verbal reports on our internal states, but it tells us very little about why there should be a subjective experience behind these reports. Like other reductionist theories, Dennett's is a theory of the easy problems.

The critical common trait among these easy problems is that they all concern how a cognitive or behavioral function is performed. All are ultimately questions about how the brain carries out some task—how it discriminates stimuli, integrates information, produces reports and so on. Once neurobiology specifies appropriate neural mechanisms, showing how the functions are performed, the easy problems are solved.

The hard problem of consciousness, in contrast, goes beyond problems about how functions are performed. Even if every behavioral and cognitive function related to consciousness were explained, there would still remain a further mystery: Why is the performance of these functions accompanied by conscious experience? It is this additional conundrum that makes the hard problem hard.

The Explanatory Gap

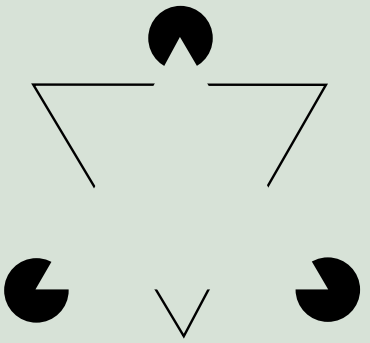
SOME HAVE SUGGESTED that to solve the hard problem, we need to bring in new tools of physical explanation: nonlinear dynamics, say, or new discoveries in neuroscience, or quantum mechanics. But these ideas suffer from exactly the same difficulty. Consider a proposal from Stuart R. Hameroff of the University of Arizona and Roger Penrose of the University of Oxford. They hold that consciousness arises from quantum-physical processes taking place in microtubules, which are protein structures inside neurons. It is possible (if not likely) that such a hypothesis will lead to an explanation of how the brain makes decisions or even how it proves mathematical theorems, as Hameroff and Penrose suggest. But even if it does, the theory is silent about how these processes might give rise to con-

information expressed by the firing of the neurons associated with color experience, at some level in the visual hierarchy.

It is not possible, then, to convey with words and ideas the exact nature of a subjective experience. It is possible, however, to convey a difference between subjective experiences—to distinguish between red and orange, for example. This is possible because a difference in a high-level visual cortical area will still be associated with a difference in the motor stages. The implication is that we can never explain to other people the subjective nature of any conscious experience, only its relation to other ones.

The other two questions, concerning why we have conscious experiences and what leads to specific ones, appear more difficult. Chalmers proposes that they require the introduction of "experience" as a fundamental new feature of the world, relating to the ability of an organism to process information. But which types of neuronal information produce consciousness? And what makes a certain type of information correspond to the blueness of blue, rather than the greenness of green? Such problems seem as difficult as any in the study of consciousness.

We prefer an alternative approach, involving the concept of "meaning." In what sense can neurons that explicitly code for a face be said to convey the meaning of a face to the rest of the brain? Such a property must relate to the cells' projective field—the pattern of synaptic connections to neurons that code explicitly for related concepts. Ultimately, these connections extend to the motor output. For example, neurons responding to a certain face might be connected to ones expressing the name of the person whose face it is and to others for her voice, memories involving her and so on. Such associations among neurons must be behaviorally useful—in other words, consistent with feedback from the body and the external world.



KANIZSA TRIANGLE stimulates neurons that code explicitly for such illusory contours.

Meaning derives from the linkages among these representations with others spread throughout the cortical system in a vast associational network, similar to a dictionary or a relational database. The more diverse these connections, the richer the meaning. If, as in our previous example of prosopagnosia, the synaptic output of such face neurons were blocked, the cells would still respond to the person's face, but there would be no associated meaning and, therefore, much less experience. Therefore, a face would be seen but not recognized as such.

Of course, groups of neurons can take on new functions, allowing brains to learn new categories (including faces) and associate new categories with existing ones. Certain primitive associations, such as pain, are to some extent inborn but subsequently refined in life.

Information may indeed be the key concept, as Chalmers suspects. Greater certainty will require consideration of highly parallel streams of information, linked—as are neurons—in complex networks. It would be useful to try to determine what features a neural network (or some other such computational embodiment) must have to generate meaning. It is possible that such exercises will suggest the neural basis of meaning. The hard problem of consciousness may then appear in an entirely new light. It might even disappear.

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scious experience. Indeed, the same problem arises with any theory of consciousness based only on physical processing.

The trouble is that physical theories are best suited to explaining why systems have a certain physical structure and how they perform various functions. Most problems in science have this form; to explain life, for example, we need to describe how a physical system can reproduce, adapt and metabolize. But consciousness is a different sort of problem entirely, as it goes beyond the scientific explanation of structure and function.

Consciousness is a different sort of problem, as it goes beyond explanations of structure and function.

Of course, neuroscience is not irrelevant to the study of consciousness. For one, it may be able to reveal the nature of the neural correlate of consciousness—the brain processes most directly associated with conscious experience. It may even give a detailed correspondence between specific processes in the brain and related components of experience. But until we know why these processes give rise to conscious experience at all, we will not have crossed what philosopher Joseph Levine has called the explanatory gap between physical processes and consciousness. Making that leap will demand a new kind of theory.

In searching for an alternative, a key observation is that not all entities in science are explained in terms of more basic entities. In physics, for example, spacetime, mass and charge (among other things) are regarded as fundamental features of the world, as they are not reducible to anything simpler. Despite this irreducibility, detailed and useful theories relate these entities to one another in terms of fundamental laws. Together these features and laws explain a great variety of complex and subtle phenomena.

A True Theory of Everything

IT IS WIDELY BELIEVED that physics provides a complete catalogue of the universe's fundamental features and laws. As physicist Steven Weinberg puts it in his 1992 book *Dreams of a Final Theory,* the goal of physics is a "theory of everything" from which all there is to know about the universe can be derived. But Weinberg concedes that there is a problem with consciousness. Despite the power of physical theory, the existence of consciousness does not seem to be derivable from physical laws. He defends physics by arguing that it might eventually explain what he calls the objective correlates of consciousness (that is, the neural correlates), but of course to do this is not to explain consciousness itself. If the existence of consciousness cannot be derived from physical laws, a theory of physics is not a true theory of everything. So a final theory must contain an additional fundamental component.

Toward this end, I propose that conscious experience be considered a fundamental feature, irreducible to anything more basic. The idea may seem strange at first, but consistency seems to demand it. In the 19th century it turned out that electromagnetic phenomena could not be explained in terms of previously known principles. As a consequence, scientists introduced electromagnetic charge as a new fundamental entity and studied the associated fundamental laws. Similar reasoning should be applied to consciousness. If existing fundamental theories cannot encompass it, then something new is required.

Where there is a fundamental property, there are fundamental laws. In this case, the laws must relate experience to elements of physical theory. These laws will almost certainly not interfere with those of the physical world; it seems that the latter form a closed system in their own right. Rather the laws will serve as a bridge, specifying how experience depends on underlying physical processes. It is this bridge that will cross the explanatory gap.

Thus, a complete theory will have two components: physical laws, telling us about the behavior of physical systems from the infinitesimal to the cosmological, and what we might call psychophysical laws, telling us how some of those systems are associated with conscious experience. These two components will constitute a true theory of everything.

Supposing for the moment that they exist, how might we uncover such psychophysical laws? The greatest hindrance in this pursuit will be a lack of data. As I have described it, consciousness is subjective, so there is no direct way to monitor it in others. But this difficulty is an obstacle, not a dead end. For a start, each one of us has access to our own experiences, a rich trove that can be used to formulate theories. We can also plausibly rely on indirect information, such as subjects' descriptions of their experiences. Philosophical arguments and thought experiments also have a role to play. Such methods have limitations, but they give us more than enough to get started.

These theories will not be conclusively testable, so they will inevitably be more speculative than those of more conventional scientific disciplines. Nevertheless, there is no reason they should not be strongly constrained to account accurately for our own first-person experiences, as well as the evidence from subjects' reports. If we find a theory that fits the data better than any other theory of equal simplicity, we will have good reason to accept it. Right now we do not have even a single theory that fits the data, so worries about testability are premature.

We might start by looking for high-level bridging laws, connecting physical processes to experience at an everyday level. The basic contour of such a law might be gleaned from the observation that when we are conscious of something, we are generally able to act on it and speak about it—which are objective, physical functions. Conversely, when some information is directly available for action and speech, it is generally con-

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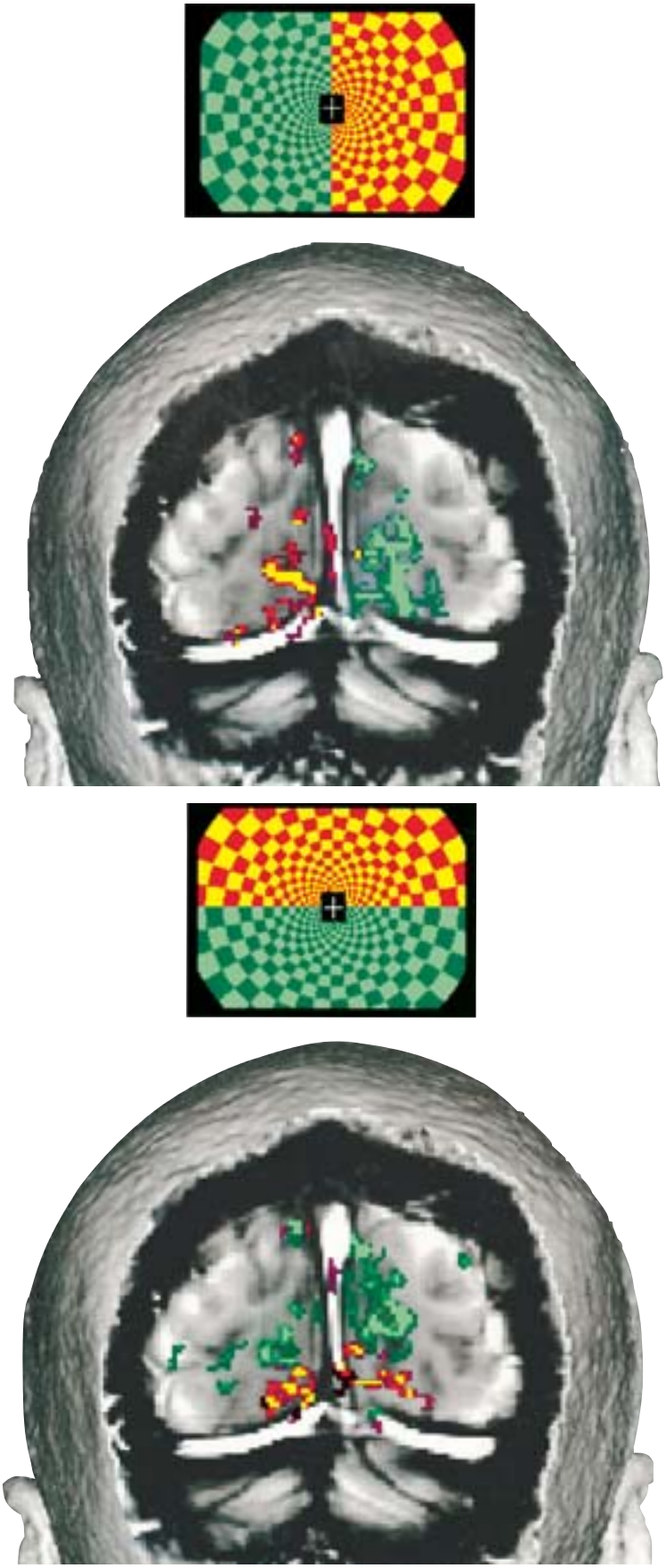
scious. Thus, consciousness correlates well with what we might call "awareness": the process by which information in the brain is made globally available to motor processes such as speech and bodily action.

Objective Awareness

THE NOTION may seem trivial. But as defined here, awareness is objective and physical, whereas consciousness is not. Some refinements to the definition of awareness are needed, in order to extend the concept to animals and infants, which cannot speak. But at least in familiar cases, it is possible to see the rough outlines of a psychophysical law: where there is awareness, there is consciousness, and vice versa.

To take this line of reasoning a step further, consider the structure present in the conscious experience. The experience of a field of vision, for example, is a constantly changing mosaic of colors, shapes and patterns and as such has a detailed geometric structure. The fact that we can describe this structure, reach out in the direction of many of its components and perform other actions that depend on it suggests that the structure corresponds directly to that of the information made available in the brain through the neural processes of objective awareness.

Similarly, our experiences of color have an intrinsic three-dimensional structure that is mirrored in the structure of information processes in the brain's visual cortex. This structure is illustrated in the color wheels and charts used by artists. Colors are arranged in a systematic pattern—red to green on one axis, blue to yellow on another, and black to white on a third. Colors that are close to one another on a color wheel are experienced as similar [*see illustration on page 100*]. It is extremely likely that they also correspond to similar perceptual representations in the brain, as one part of a system of complex three-dimensional coding



BLOOD FLOW variations in the visual cortex demonstrate how a subject's brain responds to a pattern being viewed. The colors in this image show the cortical activity corresponding to the subject's view of either the vertical or horizontal half of the pattern. The experiment may illuminate a neural correlate of visual consciousness.

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among neurons that is not yet fully understood. We can recast the underlying concept as a principle of structural coherence: the structure of conscious experience is mirrored by the structure of information in awareness, and vice versa.

Another candidate for a psychophysical law is a principle of organizational invariance. It holds that physical systems with the same abstract organization will give rise to the same kind of conscious experience, no matter what they are made of. For example, if the precise interactions between our neurons could be duplicated with silicon chips, the same conscious experience would arise. The idea is somewhat controversial, but I believe it is strongly supported by thought experiments describing the gradual replacement of neurons by silicon chips [*see box below*]. The remarkable implication is that consciousness might someday be achieved in machines.

Theory of Consciousness

THE ULTIMATE GOAL of a theory of consciousness is a simple and elegant set of fundamental laws, analogous to the fundamental laws of physics. The principles described above are unlikely to be fundamental, however. Rather they seem to be high-level psychophysical laws, analogous to macroscopic principles in physics such as those of thermodynamics or kinematics. What might the underlying fundamental laws be? No one really knows, but I don't mind speculating.

I suggest that the primary psychophysical laws may centrally involve the concept of information. The abstract notion of information, as put forward in the 1940s by Claude E. Shannon of the Massachusetts Institute of Technology, is that of a set of separate states with a basic structure of similarities and differences between them. We can think of a 10-bit binary code as an information state, for example. Such information states can be embodied in the physical world. This happens whenever they correspond to physical states (voltages, say) and when differences between them can be transmitted along some pathway, such as a telephone line.

DANCING QUALIA IN A SYNTHETIC BRAIN

Whether consciousness could arise in a complex, synthetic system is a question many people find intrinsically fascinating. Although it may be decades or even centuries before such a system is built, a simple thought experiment offers strong evidence that an artificial brain, if organized appropriately, would indeed have precisely the same kind of conscious experiences as a human being.

Consider a silicon-based system in which the chips are organized and function in the same way as the neurons in your brain. That is, each chip in the silicon system does exactly what its natural analogue does and is interconnected to surrounding elements in precisely the same way. Thus, the behavior exhibited by the artificial system will be exactly the same as yours. The crucial question is: Will it be conscious in the same way that you are?

IN THIS THOUGHT EXPERIMENT, an apple's color might flash from red to blue.

Let us assume, for the purpose of argument, that it would not be. (Here we use a reasoning technique known as reductio ad absurdum, in which the opposite hypothesis is assumed and then shown to lead to an untenable conclusion.) That is, it has either different experiences—an experience of blue, say, when you are seeing red—or no experience at all. We will consider the first case; the reasoning proceeds similarly in both cases.

Because chips and neurons have the same function, they are interchangeable, with the proper interfacing. Chips therefore can replace neurons, producing a continuum of cases in which a successively larger proportion of neurons are replaced by chips. Along this continuum, the conscious experience of the system will also change. For example, we might replace all the neurons in your visual cortex with an identically organized version made of silicon. The resulting brain, with an artificial visual cortex, will have a different conscious experience from the original: where you had previously seen red, you may now experience purple (or perhaps a faded pink, in the case where the wholly silicon system has no experience at all).

Both visual cortices are then attached to your brain, through a two-position switch. With the switch in one mode, you use the natural visual cortex; in the other, the artificial cortex is activated. When the switch is flipped, your experience changes from red to purple, or vice versa. When the switch is flipped repeatedly, your experiences "dance" between the two different conscious states (red and purple), known as qualia.

Because your brain's organization has not changed, however, there can be no behavioral change when the switch is thrown. Therefore, when asked about what you are seeing, you will say that nothing has changed. You will hold that you are seeing red and have seen nothing but red—even though the two colors are dancing before your eyes. This conclusion is so unreasonable that it is best taken as a reductio ad absurdum of the original assumption—that an artificial system with identical organization and functioning has a different conscious experience from that of a neural brain. Retraction of the assumption establishes the opposite: that systems with the same organization have the same conscious experience. *—D.J.C.*

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We can also find information embodied in conscious experience. The pattern of color patches in a visual field, for example, can be seen as analogous to that of the pixels covering a display screen. Intriguingly, it turns out that we find the same information states embedded in conscious experience and in underlying physical processes in the brain. The three-dimensional encoding of color spaces, for example, suggests that the information state in a color experience corresponds directly to an information state in the brain. Thus, we might even regard the two states as distinct aspects of a single information state, which is simultaneously embodied in both physical processing and conscious experience.

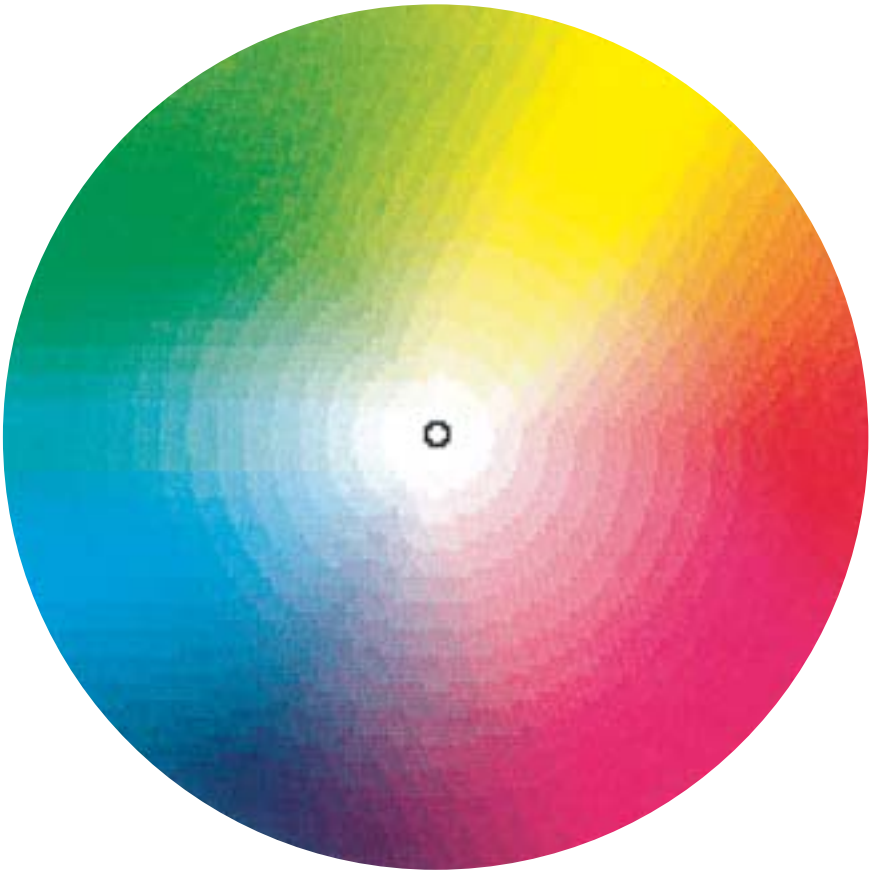
Aspects of Information

A NATURAL HYPOTHESIS ensues. Perhaps information, or at least some information, has two basic aspects: a physical one and an experiential one. This hypothesis has the status of a fundamental principle that might underlie the relation between physical processes and experience. Wherever we find conscious experience, it exists as one aspect of an information state, the other aspect of which is embedded in a physical process in the brain. This proposal needs to be fleshed out to make a satisfying theory. But it fits nicely with the principles mentioned earlier—systems with the same organization will embody the same information, for example—and it could explain numerous features of our conscious experience.

The idea is at least compatible with several others, such as physicist John A. Wheeler's suggestion that information is fundamental to the physics of the universe. The laws of physics might ultimately be cast in informational terms, in which case we would have a satisfying congruence between the constructs in both physical and psychophysical laws. It may even be that a theory of physics and a theory of consciousness could eventually be consolidated into a single grander theory of information.

A potential problem is posed by the ubiquity of information. Even a thermostat embodies some information, for example, but is it conscious? There are at least two possible responses. First, we could constrain the fundamental laws so that only some information has an experiential aspect, perhaps depending on how it is physically processed. Second, we might bite the bullet and allow that all information has an experiential aspect—where there is complex information processing, there is complex experience, and where there is simple information processing, there is simple experience. If this is so, then even a thermostat might have experiences, although they would be much simpler than even a basic color experience, and there would certainly be no accompanying emotions or thoughts. This seems odd at first, but if experience is truly fundamental, we might expect it to be widespread. In any case, the choice between these alternatives should depend on which can be integrated into the most powerful theory.

Of course, such ideas may be all wrong. On the other hand, they might evolve into a more powerful proposal that predicts the precise structure of our conscious experience from physical processes in our brains. If this project succeeds, we will have good reason to accept the theory. If it fails, other avenues will be pursued, and alternative fundamental theories may be developed. In this way, we may one day resolve the greatest mystery of the mind. SA



COLOR WHEEL arranges hues so that ones experienced as similar are closest. Nearby colors also correspond to similar perceptual representations in the brain.

MORE TO EXPLORE

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